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SOME EXPERIMENTAL OBSERVATIONS PERTI- NENT TO THE TREATMENT OF HEPATIC DISEASE*

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OUR fundamental knowledge of the functions of the liver is based on physiologic studies of that organ. We have learned from observation of animals after complete removal of the liver that this organ is essential for the maintenance of the sugar of the blood. Jaundice develops in hepatectomized animals, but the liver is necessary to convert bilirubin which reacts indirectly to the van den Bergh test to direct reacting bilirubin.

Many other metabolic processes have been shown to be entirely dependent on the liver.¹ Such functions are but rarely found to be materially impaired in the presence of hepatic disease as seen clinically. Explanation of the adequacy of these fundamental hepatic functions in the presence of extensive hepatic disease is afforded by experiments which show that more than 80 per cent of the liver can be removed from animals without demonstrable impairment of these functions. Further explanation is afforded by the fact that regeneration of the liver occurs rapidly after its partial removal or destruction by toxic agents. It should be noted also that hepatic regeneration is inhibited by the presence of jaundice, continued administration of hepatotoxic agents, or by a reduction of the blood supply to the liver.²

Studies in experimental pathology of acute, subacute and chronic hepatic degeneration produced by toxic agents such as carbon tetrachloride appear to show many similarities to hepatic disease as it occurs in human beings. Most of the experimental conditions can be clearly defined, and definite factors can be shown to influence the development and course of experimental lesions. While our knowledge of hepatic disease, both clinical and experimental, is not sufficiently complete to warrant dogmatic application of experimental observations to the treatment of hepatic disease, the factors which may be shown to influence experimental hepatic lesions should indi-

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cate general principles applicable to the treatment of disease of the liver in human beings.

Most of the observations which I will discuss were made on dogs which were given carbon tetrachloride, either by stomach tube or by inhalation. An overwhelming amount of this drug produces deep narcosis and immediate death from respiratory failure. With small doses, acute necrosis of the liver occurs, the extent of which may vary with the amount of the drug administered and be greatly influenced by the nutritive condition of the animal at the time the drug is given. Several hours after administration of carbon tetrachloride, the animal loses its appetite and emesis may occur. Jaundice is usually evident on the second day, and the animal becomes more stuporous until death occurs. If the animal survives beyond three or four days, complete recovery usually occurs; during the first few days extensive necrosis and fatty changes take place in the liver, but complete repair occurs within about two weeks and the liver appears almost normal histologically. Repeated administration of carbon tetrachloride at intervals of less than two weeks produces more chronic lesions of the liver, similar to those found in portal types of cirrhosis. After several months ascites, bilirubinemia, collateral circulation and other evidences of cirrhosis are present, and unless the course is altered such animals die from hemorrhage into the gastrointestinal tract or from a gradually progressing toxemia associated with a more or less stuporous condition.

The size and chemical composition of the liver may be greatly varied in normal animals by adherence to an unbalanced diet. Large differences ensue, especially in the glycogen, fat and water content of the liver, depending on the excess or deficiency of carbohydrate, fat, or proteins in the diet. Except when extreme conditions obtain, the ordinary functioning capacity of the liver does not appear to be disturbed. When additional stress is placed on the liver, as by the repeated administration of carbon tetrachloride, differences in function become apparent. The difference is clearly illustrated in the following experiment: Sixteen dogs, of approximately the same size, each received 10 c.c. of carbon tetrachloride by mouth daily for the duration of the experiment. Four were maintained on a diet containing about 90 per cent carbohydrate, four received a mixed diet of approximately 50 per cent carbohydrate and 25 per cent each of protein and fat, four received lean meat only, and four received a diet consisting of 80 per cent fat and 10 per cent each of carbohydrate and protein. At the end of three weeks all four of the fat-fed animals were dead. Necropsy revealed each to be icteric, the liver appeared enlarged and fatty, and numerous areas of degeneration were present in sections of the liver. At the end of one month one of the meat-fed animals had marked ascites and died two weeks later. Within three months another of the meat-fed animals died with marked ascites and the other two had definite ascites but otherwise appeared to be in good condition. In the same period the other eight dogs remained in good condition and showed no signs of ascites. Biopsy specimens of the

liver of the meat-fed animals at the end of three months disclosed that they had suffered more extensive injury than was present in the other animals, although all showed some evidence of early cirrhosis. In six to eight months the hepatic lesions of the other animals appeared about the same as those of the meat-fed animals at three months.

The effects of alcohol in the production of experimental cirrhosis are less clearly defined. We have given alcohol to the stage of definite intoxication to dogs twice daily for more than two years. Those animals which took a well-balanced diet during this time showed no gross or microscopic hepatic abnormalities. In animals receiving carbon tetrachloride and alcohol, acute hepatic degenerative changes developed rapidly and cirrhosis developed with less carbon tetrachloride than was necessary without the alcohol. We had interpreted this effect as perhaps being due to the greater solubility of carbon tetrachloride in alcohol, with the consequent more rapid absorption of effective amounts of carbon tetrachloride; but we have recently altered this view because of new evidence regarding the effect of alcohol on the liver. Alcohol in the presence of an adequate diet produces no demonstrable effect on the liver, but when food is withheld or when diets predominantly fat are given with the alcohol, the liver rapidly becomes fatty. With a fat diet that would produce fatty livers in dogs in from six to eight weeks, the addition of alcohol causes the liver to become fatty in two or three days. It is quite probable that alcohol may in a like manner increase the susceptibility of the liver to other toxic agents.

We have called attention to the fact that on examination of animals which have died from extensive hepatic injury, regardless of the methods by which it was produced, the investigator does not find the typical symptoms or the chemical changes that are found following complete removal of the liver.³ The detoxicating function of the liver appears to be depressed by changes in the organ so that the susceptibility to toxic agents is responsible for the symptoms shown, and usually the animal succumbs before the entire function of the liver is lost. When the toxic agent has destroyed part of the liver, some of the toxic substances present may be of metabolic origin and are somewhat related to the autolytic disintegration products of injured hepatic tissue. These considerations seem particularly applicable to animals with hepatic lesions which do not appear to be very detrimental to the animal under ordinary conditions but which cause it to fail rapidly following a surgical procedure which would be of no consequence to a normal animal. Following operation, these animals are markedly lacking in resistance, and extensive degenerative changes may rapidly occur in the previously injured liver.

That the condition of the liver may alter the effect of various toxic agents can be shown in a number of ways. Intoxication with alcohol may be produced in dogs with fatty livers by half the amount required to produce the same degree of intoxication in normal animals. Anesthesia with the various barbiturate derivatives is produced with about half of the amount

necessary for normal animals. The immediate effect of carbon tetrachloride is also greatly increased and the extent of hepatic damage produced is greater. In each of these examples the response to the toxic agent is similar in quality, but the quantitative response is greater the more the liver is impaired.

From an experimental standpoint certain measures have been shown to be of value in combating the fatal toxemia that follows the administration of hepatotoxic agents. The prophylactic value of diets containing large amounts of carbohydrate has been mentioned, and in combating the acute toxic effects of hepatotoxic agents, the administration of carbohydrates is of definite value. Since food is seldom taken when the animals are acutely ill, glucose given intravenously has seemed to us to have been a life saving measure when animals would otherwise have died of acute carbon tetrachloride poisoning. It is not certain just what part in maintaining the animal is played by the glucose and how much should be attributed to the fluid administered and the maintenance of renal function. Examples of the influence of carbohydrate in the diet with continued administration of carbon tetrachloride have been given. The prolonged maintenance of animals following complete biliary obstruction by means of diets rich in carbohydrate is also worthy of notice.

We have not been able to produce cirrhosis in dogs by the administration of carbon tetrachloride to the extent that ultimate symptomatic (and in part anatomic) recovery was impossible when administration of the drug was discontinued. The signs and symptoms noted in animals after the development of cirrhosis appear to be attributable to the summation of acute changes produced by carbon tetrachloride and are not immediately associated with the more permanent scarring and nodular formation in the liver. If administration of the drug is discontinued when dogs have such extreme symptoms as jaundice, emaciation and rapid accumulation of ascitic fluid, and when many tests considered as indicative of extreme damage to the liver are positive, the animals gave definite evidence of improvement within a few weeks. Within two to six months after discontinuation of the administration of carbon tetrachloride and under maintenance on a diet rich in carbohydrate, all symptoms of cirrhosis disappear, the only evidence of previous hepatic injury that persists being the collateral circulation and the appearance of gross and microscopic distortion of the hepatic lobules. Animals may then be maintained on any adequate diet, bilirubinemia is absent, ascites is absent, and there is no symptomatic or chemical change indicative of hepatic abnormality. With all tests that we have used which are considered as being tests of liver function, the reaction has approached that of the normal animal.

The occurrence of ascites in experimental cirrhosis is associated with alterations in the protein content of the serum, and the level of the serum proteins at which ascites occurs appears to be inversely proportional to the extent of hepatic damage. We have not observed ascites in cirrhotic dogs

when the serum proteins were normal. Usually there is a reduction in the total proteins of the blood, most of the decrease being due to the lowered albumin content. The plasma globulin is usually increased in respect to the albumin content and is frequently found to be present in amounts greater than that found in normal animals. The withdrawal of plasma protein by plasmapheresis hastens the onset of ascites and the lowering of the plasma proteins with the foregoing changes in composition. The regeneration of plasma proteins is less rapid when the liver is damaged but, as in the normal animal, is somewhat dependent on the proteins of the diet. The regeneration of plasma proteins in cirrhotic animals receiving a diet rich in protein is much greater than in similar animals receiving only small amounts of protein in the diet. The more rapid regeneration of plasma proteins, which occurs when the condition of the liver is improved, is more effective than the regeneration obtainable from diets rich in protein.

REFERENCES

1. BOLLMAN, J. L., and MANN, F. C.: The physiology of the impaired liver, *Ergebn. d. Physiol.*, 1936, xxxviii, 445-492.
2. MANN, F. C., FISHBACK, F. C., GAY, J. G., and GREEN, G. F.: Experimental pathology of the liver: studies III, IV, and V, *Arch. Path.*, 1931, xii, 787-793.
3. BOLLMAN, J. L., and MANN, F. C.: Alterations in hepatic function produced by experimental hepatic lesions, *Ann. Int. Med.*, 1935, ix, 617-624.

CLIMATE, MODE OF LIFE, AND HEART DISEASE*

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ARM chair philosophy in medicine has its place, but without rich experience and wisdom it can play but a minor rôle; it is wise to spend less time discussing our impressions and more time in testing their real truth.

In the field of heart disease we have been notably backward in studying carefully the results of nature's own experiments on man the world over. These clues to knowledge await us everywhere. Let me ask you some of the questions that are crying for solution.

Is it really true that coronary disease, especially early atheroma and thrombosis, is becoming more and more common among the young, well-fed, physically indolent, heavy smokers in our northern cities while it passes by the young and middle-aged hard-working farmers and laborers the world over? Is it most prevalent among Hebrews?

Let me interpolate here a question about the effect of tobacco, a topic of perennial interest. Raymond Pearl¹ recently found that heavy smokers live shorter lives than non-smokers but can we blame the tobacco itself necessarily for this? Isn't it just as probable that persons who are intemperate in the use of tobacco are more likely to be intemperate in other respects as well, thereby jeopardizing their health?

Is it simply so-called wear and tear that is responsible for the increasing mortality of our young and middle-aged men from coronary disease, or are there not other causes, at present obscure, that in some manner result from the modern way of life? Why is it that under the age of 40 years the incidence of coronary disease is twenty-four times greater among males than among females?

Does it really harm the arteries to eat diets rich in cream and butter and eggs, no matter what the age or nutritional state? Are we perchance over-feeding our youth in the course of developing a new generation of robust girls and boys? Are we swinging too far from the true and fancied evils of undernutrition in our routine diets of adult life, particularly for sedentary workers? Would it not be wise to return to an occasional fast day? Should not man earn his food physically?

Does regular and adequate exercise really promote health and prolong life as the ancients taught, as theory suggests, and as some of us believe, or is that idea another old wives' tale?

Is it not the loss of muscle tone and of active metabolism rather than the inhalation of exhaust gases that is a pernicious result of our excessive use of motor cars today? Would not our hearts and our brains and our stomachs, as well as our muscles and pocketbooks and city streets benefit by the resumption of the use of our legs either in walking or in cycling, with

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the relegation of our motor cars to special occasions when it is really necessary or advisable to use them?

Is it really true that high blood pressure is rare or even nonexistent among the Negroes in Central Africa while it is commoner among the Negroes in our Southern states than in any other group of people in the world? How much hypertension is there among the native Chinese, Arabs, Vermont farmers, New York brokers, Canadian trappers, and Esquimaux?

Does syphilitic aortitis vary in incidence fifty-fold in different communities in various parts of the world?

Is it really true, as many now believe, that the rheumatic infection and mitral stenosis, so common with us, are practically unknown in the tropics?

Is not our stimulating northern or so-called temperate climate actually favorable in its effect on our heart and arteries as well as on our muscles and mental processes, provided we avoid some of its associated evils of over-eating, overwork, and crowding the days and nights through fear that we are missing something that others are doing? Is not such a climate really an asset if we exclude the rheumatic involvement of the heart and these other handicaps I have just cited? Is it necessary to live on a tropic island to be contented and healthy? How often one hears the lament of an overtired man or his wife about the strain of our climate. Is this not simply an unjust accusation due to the unsatisfactory adjustment of life to the many demands of business, profession, family, cultural education, entertainment, sport, and social engagements which crowd every waking hour? Is it not our fault, rather than that of the climate, if high blood pressure and coronary disease and neurocirculatory asthenia and neuroses, cardiac or otherwise, assail us in early life or in middle age?

Was not Ray Lyman Wilbur² right when he recently wrote as follows: "Most people have but little idea of how to care for their bodies, or use their brains or be well enough to be happy. . . . The doctors themselves are not always good examples, and many of them care for their automobiles better than they do for themselves." In line with what Dr. Wilbur wrote it has become common knowledge that the physicians are often the earliest victims and the greatest sinners in these very things which they are trying to prevent and to control among their patients. The community at large and often even the doctors themselves do not always appreciate the heavy strain that is shouldered with seeming nonchalance by the doctor who deals all day long with the ills of humanity, spiritual and mental as well as physical. The actively practising physician requires more real leisure for the maintenance of his own good health than do most other individuals in professional and business life. A healthy personal program with ample sleep and exercise does not fit the present scheme of demands, professional and social, on the busy doctor of today. It must in some way be made to fit, for the health of the doctor is truly one of the important problems which face the medical profession in this country.

Let me ask you one more question, an ever intriguing one. What in-

fluence does the weather have in any given climate on the incidence of heart disease or on the symptoms thereof? May not the weather be too stable for the maintenance of a perfect circulation? Can one blame heart disease or heart attacks on low barometric pressure or on high, on high humidity or on low, on too much wind velocity or on too little, on too little rainfall or on too much, on too cold a day or on too hot? Attempts in this direction have been made, for the most part unsuccessfully, since ancient days. I myself realized the almost hopeless tangle and confusion, except in rare cases, when I tried with Dr. Brasil to make a preliminary analysis a few years ago of the relationship of acute illness and death among my cardiac patients to the multitudinous weather factors alone and in various combinations. There are to be sure a few simple observations that are well known, chiefly that of the production of angina pectoris by walking against a cold wind, but the great majority of the other correlations are almost pure guesses, and naturally so, in view of the interplay of a host of other factors besides the many of the weather acting on any one patient at any given moment. There are too many variables that are more important than the weather variables themselves to draw many conclusions in the present state of our knowledge. To our surprise, for example, we found that our cases of acute coronary thrombosis occurred more or less uniformly throughout the year with little or no regard to heat or cold, sun or rain, wind or calm; there may have been some intricate or hidden effect of weather, but it will take years of carefully controlled investigation of thousands of cases to unravel them. It may be that the sunspots, aurora borealis, and position of the constellations have a bearing on heart disease and some day it may be so shown, but for the present at least and for the immediate future it appears to be more profitable to study the more potent factors of the mode of life, diet, work, infection, familial and racial inheritance, and climate in general in their bearing on heart disease.

Are there any adequate answers to the important questions I've asked? No. We have our impressions from years of practice or observation, there are meager statistics on certain points here and there, and we have had hopes of studying the problems more intensively. But actually little has been done. In 1934 I attended the triennial congress of the International Association of Geographic Pathologists in Holland. The subject was arteriosclerosis. Many of the world's leaders in pathology and in vascular disease were present but the results were most disappointing. There was but the vaguest idea of the incidence of arteriosclerosis throughout the world. The same thing would probably be true of hypertension, rheumatic valvular disease, and luetic aortitis if there were now to be held international meetings on these subjects.

I have looked through such an extensive survey as McKinley's *Geography of Disease* (1935)³ based on official health records from all parts of the world but there is disappointingly little about the etiological factors behind heart disease, although much about the great scourges of days past

—tuberculosis, typhoid, and malaria. There are to be sure some interesting estimates to speculate about, but it is obvious that careful study is still needed almost everywhere to feel at all sure about the general incidence of various etiological factors, leaving out of consideration altogether the relative incidence among various different groups in any community. In Hawaii, for example, rheumatic fever is said to be rare while valvular lesions are noted as common; is that because luetic aortitis is a frequent occurrence or is it because the rheumatic infection escapes notice? Hypertension and cardiovascular disease are said to be common in Hawaii; are they related, or is there also a lot of coronary disease there? On the other hand in the Philippines in 1934 rheumatic fever was blamed for 318 deaths, one-third as many as all the deaths from cardiovascular disease in that year; can we feel sure about that ratio? In Puerto Rico in 1933 hypertension was noted as common and valvular heart disease as rare, while in Uganda in that same year only three cases of hypertension were noted as against 485 of valvular disease; if these figures are reliable, what is the reason for such differences? In China in 1934 rheumatic fever was reported as rare in the north and common in the center and south, the opposite of our findings in the United States; is this true? Coronary disease, one of the most important of all factors, is barely mentioned in any of the statistics.

Dr. Takahashi of the Imperial Household in Tokyo kindly sent me the Japanese Health Report for 1934.⁴ I was especially interested in the diagnosis of coronary disease as a cause of death in the various age groups; between 30 and 40 years of age and between 70 and 80 it was responsible for about $\frac{1}{2}$ per cent of the deaths, between 40 and 70 quite uniformly for about 1 per cent, and after 90 years for less than $\frac{1}{10}$ per cent. In the United States, on the other hand, the vital statistics for the same year 1934 gave the diagnosis of coronary disease or angina pectoris as a cause of death in a much higher percentage of cases; thus nearly 2 per cent between the ages of 30 and 40, 4 per cent between 40 and 50, over 6 per cent between 50 and 70, 5 per cent between 70 and 80, and only $\frac{2}{10}$ per cent after 90. Is it really true that in the very important age period between 50 and 70 coronary disease kills relatively six times as many persons in the United States as in Japan? If so, what is the reason? It is not to be ascribed to a disproportion of the mortality by decades in the two countries, for the total mortality runs parallel in the United States and Japan, being greatest in each country between 70 and 80 and next greatest between 60 and 70.

Incidentally Dr. Takahashi told me that it was his conviction that hypertension had increased very much in Japan in the last two decades; this increase he ascribed to the introduction of the occidental mode of life. Meanwhile beri-beri has become relatively rare.

A good deal of analysis of the relative incidence of the types of cardiovascular disease in the more advanced parts of the world has been made and they are already worthy of comparison but we are still largely ignorant of the absolute incidence and of the situation among various groups in any one

community—a very vital point. Dr. Cossio of the Argentine has just sent me some interesting data concerning 4,000 cardiac patients which he has analyzed and also some impressions concerning the community incidence. Of the 4,000 cases he has labelled 22 per cent as functional in comparison with 20 per cent of 3,000 cases which we studied in New England,⁵ 22 per cent he called coronary in contrast to 28 per cent of our own, 20 per cent of the Argentine group were hypertensive compared with 24 per cent in New England, only 14 per cent were rheumatic in contrast to our largest percentage of 32, 6 per cent were luetic which is twice the percentage that we found, and the balance of 16 per cent included congenital and thyrotoxic cases, the cor pulmonale, bacterial endocarditis, trauma, and so forth, compared with 10 per cent of our group.* This interesting comparison between the United States and the Argentine Republic is a beginning, but really only the first step, in the solution of the problem. Dr. Cossio goes on to say a word or two about the more important aspects of the question. He finds, for example, as we do, that rheumatic heart disease is more frequent in hospital than in private practice, that arterial hypertension is more frequent in the city workers and big business men than in the farmers and camp workers, and that rheumatic fever is more common in the cold damp parts of the country than in the warm or cold dry parts.

Finally, I have written to various other reliable workers in near and distant parts of the world for statements as to their knowledge or impressions of the incidence of cardiovascular disease in their countries and particularly in different groups in their own communities. All have responded in a most coöperative way, expressing their great interest in the subject which they regard as of fundamental importance, but at the same time they disclaim any accurate knowledge. Their impressions, however, are often illuminating and pave the way for further study. Let me read you a few sentences from the reply of one of these collaborators of mine, Paul Harrison, who is in charge of the American Mission Hospital at Muscat on the Persian Gulf; it is characteristic and to my mind especially illuminating as suggestive of the relatively low incidence of heart disease among the coastal and desert peoples of eastern Arabia. He writes: "I cannot discuss the questions you put in the way I wish I could. We live in a subtropical area here with the heat in the summer fairly extreme, and the humidity at times very high, the sea being next door. At times, and in fact usually, our air is dry, for our rainfall is extremely low, under four inches rather than above, on the average. Years vary. I have seen as high as six. This year we have not yet had a quarter of one inch and the usual season for rain is over. Last year I doubt if we reached an inch.

"Living conditions in our so-called cities are not significantly different than in the somewhat smaller outlying villages which house the date gardeners. Malaria is the common disease, and is nearly universal. It has

* There is a slight discrepancy in the figures in that Cossio's add up to 100 per cent and ours to 117 per cent because we included cases showing multiple diagnoses in the separate categories.

the expected result of large spleens and anemia. Hours are long and the work laborious, inasmuch as labor saving machines are nearly unknown. On the other hand the mental tension is low and nobody takes his work to bed with him.

"The remarks above apply to the oasis dwellers who constitute, I imagine, three-quarters of our population, i.e. the population of the province of Oman. In addition there are the nomads whom we term Bedouins. These are goat raisers of a very limited type. The Bedouins suffer very little from malaria.

"With this much of an introduction it is easier to say what we can of the various problems you mention. The stethoscope and the sphygmomanometer are what we have to work with. Of the four types which you mention (coronary, hypertensive, rheumatic, and luetic) hypertension seems very rare. We see less than a case a year on the average. . . . It is not easy to express any opinion as to whether the rural or urban communities are most affected.

"Heart disease due to syphilis is commoner than hypertension. It is a disease of the coast communities and of the oases, not so much of the Bedouins. Of severe aortic insufficiency we see about a case a year. . . . The Bedouins while suffering from syphilis very widely have developed a distinctly attenuated type. . . . The cardiovascular system is practically never affected. . . . The ports are full of syphilis which has been recently imported from the outside world for the Arabs of these port cities are great travellers. My impression is that even in these port cities the severe late syphilitic lesions are much less common than would be expected in the west. . . . Aneurysms of the aorta come in, but not frequently. In 25 years I have seen three, I believe, one of the arch and two of the abdominal aorta.

"Rheumatic heart disease is commoner than the above. Mitral lesions are at least double the number of severe aortic lesions. . . . The cases that come to us are far advanced. . . . We see two or three cases a year. It is not possible to be certain but I think that the Bedouin community is more or less free from that type of lesion. . . .

"Acute articular rheumatism we see about a half a dozen cases a year. It is usually of a mild type, and it has never been possible for me to demonstrate a murmur developed during the disease. It runs a protracted course, and several joints are usually affected, one after another before the disease runs out. My impression is very definite that this disease is increasing throughout the coast communities where our contacts are considerable.

"Colds are common through this community, especially in the spring and fall when the prevailing weather changes considerably." Finally, Harrison closes with the observation that living conditions and, in a more or less parallel manner, health conditions have been going down grade of late years because of the increasing poverty incident to the drop in the price of their chief export, dates.

Now, what is the answer to all this? It is evident at once that much

hard work remains to be done and must be done. We cannot experiment on man and we cannot always apply animal experiments satisfactorily to man. But we can make use of the many experiments that nature herself is constantly making on man. It will be possible, I am sure, when the work is done, to evaluate the effect of the various individual factors of climate, race, occupation, diet, and disease on the heart. We can have thousands of cases in which all these essential factors will be closely similar except for the one that is under scrutiny at the moment; for example, how do Chinese laborers or English business men react to different climates? How do different occupations affect one racial group in one climate? How do different races react to a certain type of diet or to a disease?

In conclusion, how may this study be carried out? Obviously by well and similarly trained teams, with good equipment and plenty of time, and with the same program of work. It would be most desirable if such a project could be effected by international effort, as by a League of Nations. It might, however, be done sooner and more practically through some foundation which has been already established for the study of disease and the promotion of public health throughout the world. Or it might be accomplished through the initiative or collaboration of universities. In any given country it might be done by the national government but such a study would be incomplete; it might begin in that way, to be sure, but for completion it would be necessary to secure smooth and effective international coöperation. Finally, it might still be the private endeavor of a group of individuals or of a single well-to-do enthusiast who is burning with the desire to be a pioneer in this vital work. Someday it will be done and medical knowledge will thereby be greatly enriched.

BIBLIOGRAPHY

1. PEARL, R.: Tobacco smoking and longevity, *Science*, 1938, lxxxvii, 216.
2. WILBUR, R. L.: March of medicine, *Science*, 1938, lxxxvii, 199.
3. MCKINLEY: A geography of disease, George Washington University Press, Washington, D. C., 1935.
4. The Annual Report of the Sanitary Bureau of the Home Department of the Imperial Japanese Government for the 10th Year of Showa (1935), Tokyo, 1937.
5. WHITE, P. D., and JONES, T. D.: Heart disease and disorders in New England, *Am. Heart Jr.*, 1928, iii, 302.

HYPERPARATHYROIDISM SIMULATING OR ASSOCIATED WITH PAGET'S DISEASE; WITH THREE ILLUSTRATIVE CASES *

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Generalized *osteitis fibrosa cystica* (von Recklinghausen's disease) and *osteitis deformans* (Paget's disease) were regarded formerly as related variants of a single skeletal disease. This concept, however, proved irreconcilable with subsequent clinical, roentgenologic, biochemical and pathologic observations and the consensus now is that generalized *osteitis fibrosa cystica* and *osteitis deformans* are discrete and unrelated entities.¹ Generalized *osteitis fibrosa cystica* has been shown to be due to hyperparathyroidism² whereas *osteitis deformans* is not due to hyperparathyroidism but to unknown, probably local, factors influencing bone metabolism.

A serious difficulty with the prevailing view, however, lies in the increasing number of patients described as presenting both hyperparathyroidism and Paget's disease. Such cases have been variously regarded as representing transition stages from the one disease to the other,^{3, 4, 5} or as illustrating the fortuitous co-existence of both (unrelated) diseases. The former explanation has become increasingly improbable as evidence against the existence of any relation between hyperparathyroidism and Paget's disease has accumulated (table 1); and on the other hand the number of patients reported as presenting both conditions is now too large to be dismissed as mere coincidence.

This interesting group of cases was classified as "hyperparathyroidism simulating (or complicated by) Paget's disease" by Albright, Aub and Bauer,^{1d} who reported two cases. Our own observations consist of clinical, roentgenologic and biochemical studies on three similar patients with proved hyperparathyroidism presenting, in addition, certain aspects of Paget's disease. We wish to consider here the problems in interpretation and management raised by these patients in relation to the relevant cases in the literature.

CASE HISTORIES

Case 1. A. G., an American housewife, aged 51, was admitted to the Urological service of the Presbyterian Hospital in March 1931 for investigation of the genito-urinary tract because of intermittent pyuria. She had been well until 1928, when she complained of weakness, loss of 20 pounds and pain in the left flank and lower abdomen, with cloudy urine. In March 1930 the left kidney had been removed at another hospital because of nephrolithiasis with secondary pyonephrosis. Following this operation, she gained weight and felt improved, but weakness persisted. "Arthritic" pains developed in the left hip, lower back and right knee shortly thereafter, and became progressively worse. The urine again became cloudy.

* Received for publication July 20, 1937. From the Departments of Medicine and Surgery, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York.

At the time of admission to the Presbyterian Hospital, physical examination was essentially negative, apart from obesity, except for a moderately enlarged, non-tender right kidney. The urine showed a heavy trace of albumin and many pus cells. The right ureter was catheterized, yielding a steady flow of cloudy urine. Pyelograms revealed a staghorn calculus in the right kidney pelvis, with some dilatation of the pelvis and calices. The lower spine and the pelvis were visualized on these films and appeared to be normal. The blood urea nitrogen was 17.5 mg. per cent. The blood Wassermann test was negative. The patient was discharged 10 days after admission, since further surgical intervention was felt to be inadvisable.

She continued to attend the urological service as an out-patient. Lavage of the renal pelvis and various urinary antiseptics during this period failed to control the pyuria. Because of continued diffuse "arthritic" pain and stiffness in the knees,

TABLE I

Resumé of Clinical, Roentgenologic and Biochemical Findings in 150 Cases of Hyperparathyroidism and in 147 Cases of Paget's Disease,* with the Essential Pathologic Changes in These Diseases

	Hyperparathyroidism		Paget's Disease	
1. Frequency	Primary hyperparathyroidism rare		Not uncommon in persons over 40	
2. Familial incidence	Primary hyperparathyroidism not familial		Exceptional but does occur	
3. Sex distribution				
Males	37		75	
Females	113		72	
	Age at Operation or Death (No. Cases)	Age at Onset of Symptoms (No. Cases)	Age when Diagnosed (No. Cases)	Age at Onset of Symptoms (No. Cases)
4. Age distribution				
1-9 yrs.	—	2	0	0
10-19 yrs.	12	17	0	0
20-29 yrs.	20	25	1	3
30-39 yrs.	31	40	9	11
40-49 yrs.	39	36	29	36
50-59 yrs.	32	23	40	43
60-69 yrs.	12	7	51	15
70 yrs. plus	4	—	17	3
			(36 cases asymptomatic)	
	Major Early Symptoms (No. Cases)	Major Subsequent Symptoms and Signs (No. Cases)	Initial Symptoms (No. Cases)	Major Subsequent Symptoms and Signs (No. Cases)
5. Clinical symptoms and signs				
A. Skeletal				
Pain back; hips; extremities; head	71	59	50	79
Gross deformities back; extremities; bony swellings extremities; ribs; hips	41	53	21	58
Enlargement of skull	0	1	18	35
Difficulty in gait	23	21	6	43
Bedfast	3	27	0	6
Fractures	27	36	7	18
Muscle weakness	21	22	0	4
B. Renal				
Polyuria, polydipsia	9	12	0	2
Renal colic	9	4	3	1
C. Gastrointestinal				
Nausea, vomiting, anorexia	12	20	0	1
Epigastric pain	2	5	0	2
D. Miscellaneous				
Marked loss of weight	12	25	0	3
Deafness	0	1	6	33
Paresthesias, numbness legs	0	2	2	6
			(36 cases asymptomatic)	
6. Blood findings				
Hypercalcemia	Present in 4/5 of cases. Absence usually associated with renal insufficiency causing nitrogen retention and hyperphosphatemia		Absent in uncomplicated cases	

TABLE I—Continued

	Hyperparathyroidism	Paget's Disease
Hypophosphatemia	Present in about $\frac{1}{2}$ of cases. Absence usually associated with renal insufficiency, in which hyperphosphatemia may occur	Absent
Serum phosphatase activity	Almost always increased in cases with definite skeletal changes, usually to 2 to 10 times maximum normal values. Not elevated in cases without definite skeletal changes	Almost always increased, up to 40 times maximum normal value. Level roughly proportional to extent and activity of bone lesions
7. Calcium balance	In negative calcium balance on diets ordinarily adequate, due to increased urinary excretion	Within normal limits
8. Roentgenologic findings	Usually generalized decalcification with one or more bone cysts and grainy mottling of the skull. May not be apparent in early or acute cases. Occasionally, sclerotic areas due to recalcification. Renal calculi in many cases. Fractures common. Characteristic deformities	Increased density of involved bones, usually with coarsely striated trabeculations, sometimes densely sclerotic. "Cotton-wool" appearance of skull. Not generalized but may involve most bones. Typical deformities
9. Pathologic findings	One or more parathyroid tumors present. Generalized decalcification of bones, increased osteoclastic activity, occasional osteoclastomata. Some new-bone formation with increased osteoblasts. Marrow fibrosis. Occasional "brown tumors." Bones often soft, misshapen	No parathyroid tumors present. Some decalcification, but new-bone formation, irregularly laid down, predominates. Typical "mosaic" segments of lamellar bone, prominent cement lines

* With the exception of 9 proved cases of hyperparathyroidism from our own records, this summary of 150 cases of hyperparathyroidism is based upon reports in the literature. The data are adapted from the analyses of Gutman, Swenson and Parsons^{1a} and Gutman.⁶ Only cases in which one or more parathyroid tumors were found at operation or autopsy, and in which there was definite evidence of parathyroid over-activity are included.

The series of 147 cases of Paget's disease is from the records of the Presbyterian Hospital, 1915-1937. The group includes the series of 116 cases of which a more detailed analysis was published elsewhere.⁷

back and fingers, she was referred to the Arthritis Clinic in March 1932. Prominent Heberden's nodes and a non-tender swelling of the right knee with crepitus were noted there and a diagnosis of chronic hypertrophic arthritis was made. Diathermy gave no relief of pain.

Roentgenograms of the genito-urinary tract were repeated in March 1932. These showed no appreciable change since the preceding year. An incidental finding on this occasion, however, was "a peculiarity of the architecture of the left innominate bone which suggests *osteitis deformans*" (figure 1a). In April 1932 she tripped and fell upon her right knee, following which pain, swelling and, subsequently, tenderness of the upper end of the right tibia developed. She was incapacitated for one week. Difficulty in walking due to diffuse pain and stiffness progressed within the next two years so that she was able to perform only light housework.

In November 1935 (in the course of a systematic study of patients with nephrolithiasis) a sample of her blood was submitted to us by Dr. S. A. Beisler. Analysis revealed hypercalcemia, hypophosphatemia and increased serum phosphatase activity (table 2). Through the coöperation of Dr. C. I. Buttrick, the patient was admitted to the medical service of the Presbyterian Hospital in January 1936, with the provisional diagnosis of hyperparathyroidism. Her chief complaints on admission were difficulty in walking, fatiguability and pain, chiefly in the hips and knees. There had been no loss of weight or fractures.

The patient was found to be obese (74 kg.), pale and chronically ill in appearance. There was a definite rounded, non-tender dorsal kyphosis. The proximal half of the right tibia was markedly expanded and slightly tender. There were no

TABLE II

Serum Calcium, Inorganic Phosphorus, Phosphatase Activity and Non-Protein Nitrogen Before and After Operation in Three Cases of Hyperparathyroidism Simulating or Associated with Paget's Disease

Case	Date	Serum			
		Calcium (mg. %)	Inorg. P (mg. %)	Phosphatase (Bodansky units/100 c.c.)	Non-protein N (mg. %)
A. G.	11-18-35	12.3	1.9	25.3	36
	12- 2-35	13.4	1.6	26.5	36
	1-16-36	12.6	1.4	20.1	29
	1-28-36	Operation: Parathyroid tumor removed			
	1-29-36	10.3	1.4	20.8	34
	1-30-36	8.8	1.7	18.7	36
	2- 3-36	8.6	2.1	23.1	29
	2-11-36	8.1	2.6	24.8	34
	2-21-36	9.6	3.2	17.6	35
	1-19-37	9.9	2.6	13.1	37
	6-23-37	10.5	2.2	12.4	29
M. B.	12-29-34	14.0	3.0	—	—
	1- 9-35	14.5	3.0	—	—
	7- 6-36	13.7	1.8	2.9	—
	6-17-37	12.6	2.1	3.0	33
	7- 2-37	12.8	1.9	2.7	26
	7- 9-37	Operation: Parathyroid tumor removed			
	7-10-37	10.4	2.0	2.7	—
	7-12-37	9.0	2.8	2.2	30
	7-14-37	10.3	2.4	3.1	—
	7-19-37	9.5	2.7	3.3	29
L. L.	9- 8-30	10.9	—	—	—
	10- 1-35	12.9	1.9	31.4	29
	3-24-36	12.7	1.8	32.6	29
	7-14-36	11.8	2.3	35.2	29
	7-24-36	12.0	2.5	35.5	27
	10- 6-36	11.6	2.8	28.5	29
	10- 7-36	Operation: Parathyroid tumor removed			
	10- 9-36	9.5	2.9	26.5	30
	10-13-36	9.6	3.5	34.6	—
	11- 6-36	10.8	3.0	31.3	—
	12- 4-36	11.0	3.1	32.8	—
	1-19-37	10.5	2.7	31.3	28
	4-14-37	10.6	2.8	29.3	32
	4- 6-38	10.7	2.5	30.3	26

other significant findings on physical examination. The right kidney could not be palpated satisfactorily. No palpable tumor was present in the neck.

The urine contained a trace of albumin and occasional pus cells but no casts or Bence Jones protein. Phenolsulphonphthalein excretion was 35 per cent in two hours. There was no nitrogen retention. The erythrocyte and leukocyte counts and the hemoglobin content of the blood were within normal limits. Repeated analyses of the blood showed consistent hypercalcemia, hypophosphatemia and increased phosphatase activity (table 2). Roentgenograms revealed a moderate generalized decalcification of the skeleton with typical blurring of the finer bone architecture. There was a large cyst in the proximal portion of the right tibia (figure 2) and a small cystic area in the region of the medial malleolus on that side. The left side of the pelvis presented Paget-like sclerosis and coarse trabeculations, as described in 1932. These changes were now more extensive and were associated

with obvious cystic involvement (figure 1b). (On reviewing the 1932 films, cysts were recognized in the left innominate and pubic bones.) There was no mottling of the skull but two small cysts were present in the occipital region.

The calcium excretion on a low calcium diet was studied, the intake being determined by analysis of food aliquots. The patient was found to be in negative calcium balance. After a preliminary period of six days, the total excretion of calcium per 24 hours (mean of 2 three-day periods) was 0.468 gram on an intake of 0.215 gram per day. Seventy-four per cent of the total calcium excreted was in the urine (table 3).

TABLE III

Calcium Balance Studies in Three Cases of Hyperparathyroidism Simulating or Associated with Paget's Disease
(Results expressed in grams per 24 hours, the mean of 3 day periods)

Subject	Period	Ca Intake	Ca Output			Balance	% Ca in Urine Total Ca Output
			Urine	Stool	Total		
A. G.	I	.215	.349	.090	.439	-.224	79.5
	II	.215	.343	.154	.497	-.282	69.0
M. B.	I	.126	.126	.181	.307	-.181	41.0
	II	.126	.096	.354	.450	-.324	27.1
L. L.	I	.096	.432	.126	.558	-.462	77.4
	II	.094	.423	.096	.519	-.425	81.4

Exploration for parathyroid tumor was performed (W.B.P.) on January 28, 1936. Posterior to the lower pole of the right lobe of the thyroid gland, at about the level of the clavicle, an ovoid, slightly lobulated tumor measuring 4.0 by 2.5 by 1.0 cm. was found. Three normal parathyroid glands were identified in their usual locations and were not disturbed. Histologic study showed the tumor to be an adenoma of the parathyroid gland composed of a solid mass of polygonal cells which were considered to be transitional between the water-clear and chief-cell types.

Her postoperative course was uneventful. The serum calcium fell rapidly (table 2) and on the second day she complained of mild paresthesias of the extremities which were readily relieved by administration of calcium salts. No manifest tetany developed. She was discharged February 16, 1936.

Two months after operation she was able to resume housework, had gained weight and strength but still complained of some pain in the right knee. One year after operation she was in excellent condition and very active.

The serum calcium and inorganic phosphorus returned to normal levels within three weeks after operation and have remained normal (table 2). The non-protein nitrogen content of the blood showed no upward trend after operation. The phosphatase activity of the serum was not immediately affected by ablation of the parathyroid tumor but began to decline after some months, reaching a level of 12.4 Bodansky units per 100 c.c. serum after 17 months, as compared with pre-operative levels of more than 20 Bodansky units. The decrease in serum phosphatase activity in this instance was slower than in most cases, but comparable to that observed by us in one patient with proved hyperparathyroidism.⁸

Roentgen-rays taken five months after operation showed only slight recalcification. At the end of one year, however, there was a definite general increase in bone density, much of the "ground-glass" appearance having disappeared. The cystic areas of the left side of the pelvis had become largely sclerosed, with striking diffuse increase of density but without bundling of the trabeculae (figure 1c). The small

cysts in the occipital region of the skull were partially sclerotic. Early but definite sclerosis of the large cyst of the right tibia had developed.

Case 2. M. B., a Syrian woman, aged 54, unmarried, was admitted to the Presbyterian Hospital on June 14, 1937, with the diagnosis of hyperparathyroidism. Until 1924 she was well, apparently, and working regularly. In February 1924, she fell, fractured the left femur and was hospitalized because of delayed union. She has been confined to bed ever since.

When admitted to a hospital for chronic diseases in 1924, deformities and bony swellings of both legs and of the left humerus were noted. There was expansion of the terminal phalanges, with some fixation of the fingers in flexion. Roentgen-rays of the bones showed decalcification and she was diagnosed "osteomalacia." Her course during the next 13 years was characterized by the repeated occurrence of pathologic fractures of the legs, arms and ribs; and by the development of extreme deformities, particularly of the legs. She complained intermittently of pain over the bones, but this was never a prominent symptom. In 1931 and again in 1933, there were two transitory episodes of weakness and incoördination of the right arm and leg associated with partial aphasia, apparently due to cerebral hemorrhage. On one of these occasions, unilateral carpal spasm resembling tetany developed, but without response to calcium therapy. There was no history of renal colic, polyuria, polydipsia or gastrointestinal symptomatology (except constipation).

Blood studies in 1934 and 1935 (table 2) showed hypercalcemia but the serum inorganic phosphorus appeared to be within normal limits. A specimen of blood was submitted to us for examination in July 1936 by Dr. D. Seegal. On that occasion, hypercalcemia and hypophosphatemia were present. The serum phosphatase activity, however, was within normal limits (table 2).

When admitted to the Presbyterian Hospital in 1937, the patient presented a striking picture of the extreme deformities seen in advanced hyperparathyroidism. The legs were atrophied, shapeless, bizarrely deformed appendages. The pelvis was tilted to the left and distorted. There were obvious bony deformities of both arms. A rounded dorsal kyphosis of the spine was present. The sternum was thrust forward due to flattening of the bony thorax in its lateral dimension. The skull was enlarged, somewhat resembling Paget's disease. The chin rested on the sternum because of shortening of the neck. The interosseous muscles of both hands were atrophied with flexion of the distal phalanges but no obvious clubbing of the fingers. Pronounced prognathism was present without evidences of bony tumor of the jaws. The teeth were decayed, many were missing. She was not in pain when she did not move about in bed. The bones of the legs were extremely tender to pressure, however, and there was some tenderness over the ribs, spine and arms. A nodular mass was palpable in the neck on the left. A purulent discharge was draining from the right antrum. Resonance at both lung bases was slightly impaired; occasional coarse râles were heard.

The blood Wassermann test was negative. Blood counts showed no abnormalities. The urine was negative except for the intermittent appearance of a few red blood cells. The phenolsulphonphthalein excretion was 37 per cent in two hours. Hypercalcemia and hypophosphatemia, but normal serum phosphatase activity, were found consistently. After a 5-day fore-period, study of the calcium balance on a low calcium intake (ingested calcium being determined by analysis of food aliquots) showed that, unlike our cases of hyperparathyroidism, the excretion of calcium in the urine was not excessive.

Roentgen-rays of the skeleton showed generalized decalcification of extreme degree, particularly in the bones of the legs (figure 3), in which numerous cysts were present. Cysts were also found in the deformed and decalcified pelvis, and in the ribs which, like other bones, were the seat of numerous fractures. The vertebrae presented a marked "ground-glass" appearance. These skeletal changes were re-

garded as typical of advanced hyperparathyroidism. The cranial vault, on the other hand, was definitely thickened and diffusely sclerotic (figure 4). The "cotton-wool" appearance characteristic of Paget's disease was absent, however. There were no renal calculi.

Exploration on July 9, 1937 (W.B.P.) revealed a tumor 3.0 by 1.2 by 0.5 cm. inferior to the left lower pole of the thyroid gland, and extending below the manubrium. Following removal of this tumor, the serum calcium fell rapidly (table 2). Tetany did not become manifest. The mass proved to be a parathyroid adenoma composed largely of chief-cells, some transitional to the water-clear type, and many rose-red cells.

Following operation the patient gained weight and strength and now is able to get about in a wheel-chair.

Case 3. L. L., a housewife, then aged 48, came to the Presbyterian Hospital in 1930 for treatment of obesity. Physical examination revealed marked antero-lateral bowing of the right tibia, with slight tenderness. She stated that in 1920 she had developed pain in the lower back and right knee, worse on exercise. The pain in the back largely disappeared, but the knee became worse, proving refractory to physiotherapy. Progressive bowing of the right tibia was noted in 1922, with limp and increasing difficulty in gait since 1925. She thought her head had "always" been large and had not noted any recent increase in size of her hats. There was no loss of hearing. There had been no fractures, no renal colic.

Roentgen-rays of the right tibia in 1930 showed marked antero-lateral bowing with thickening of the cortex and coarse, irregular trabeculations. Areas of decreased density were also thought to be present in the mid-third of the shaft. The film was interpreted as either *osteitis fibrosa cystica* or Paget's disease. The serum calcium in 1930 was found to be normal (10.9 mg. per cent, table 2). The blood Wassermann test was negative.

In 1931 roentgenograms of the skull disclosed numerous ill-defined rounded shadows of increased density involving most of the calvarium. There was also some thickening of the floor of the anterior fossa. The changes were regarded then (and now) as typical of Paget's disease. In addition, there was in the occipital region an area of osteoporosis circumscripta, a condition commonly associated with Paget's disease. The diagnosis of Paget's disease was made. Because of persistent pain in the right tibia and also because of severe occipital headache, she received radiotherapy to the right tibia and to the skull for relief of pain. The response was unsatisfactory and she dropped out of sight.

In October 1935, in the course of a study of blood changes in *osteoporosis circumscripta*,⁹ this patient was located and serum obtained for analysis. These determinations unexpectedly showed the presence of hypercalcemia and hypophosphatemia, together with the anticipated rise in serum phosphatase activity (table 2); results suggested hyperparathyroidism rather than Paget's disease.⁸ Reëxamination of the blood in March 1936 confirmed these findings (table 2). Repeated roentgenologic studies of the entire skeleton, however, failed to disclose any generalized decalcification or cystic changes. The right tibia again presented the diffusely thickened cortex and coarsely striated trabeculae typical of Paget's disease (figure 5), with distinct distal encroachment since 1931. The characteristic "cotton-wool" appearance of the skull did not resemble the fine, grainy mottling usually seen in hyperparathyroidism. The area of *osteoporosis circumscripta* was now almost completely replaced by sclerotic bone (figure 6).

Because of these discrepancies, the patient was admitted to the medical service of the Presbyterian Hospital in July 1936 for further study. Her presenting complaints on this admission were diffuse pains in both knees, hips, arms and the lower back. Walking had become so labored and painful that she was able to negotiate only short distances. The bowing of the right tibia had progressed, causing shorten-

ing of the right leg and tilting of the pelvis. The severe occipital headaches had recurred. She complained of weakness and fatigability. There was no interval history of fractures, renal colic, polyuria, polydipsia, gastrointestinal upsets or increase in the size of the head.

Physical examination showed an obese, phlegmatic housewife of 54 years, not in acute pain so long as she remained in bed. The occipito-frontal circumference of the head was 60.5 cm., with questionable parietal bossing. Moderate mid- and upper dorsal kyphosis was present, without tenderness. There was increased antero-lateral bowing of the right tibia (figure 5), which was definitely tender. Other deformities, including clubbing of the fingers, were absent. Except for obesity (205 pounds), examination otherwise was negative. No mass could be palpated in the neck.

Blood counts and urine analysis showed no abnormalities. Hypercalcemia, hypophosphatemia and increased serum phosphatase activity were found consistently on repeated examinations (table 2). The patient was found to be in marked negative calcium balance due to excessive loss of calcium in the urine. After a preliminary period of eight days, the total excretion of calcium per 24 hours (mean of 2 three-day periods) was .539 gram on an intake of 0.095 gram of calcium per day (determined by analysis of food aliquots). Of the total calcium excreted, a mean of 79.4 per cent was in the urine. These results, typical of hyperparathyroidism, are inconsistent with the normal calcium balances found in uncomplicated Paget's disease¹⁰ (see figure 3).

Exploration for parathyroid tumor was performed (W.B.P.) on October 7, 1936. The inferior parathyroid glands on both sides were found slightly enlarged but were not disturbed. At the site of the left superior parathyroid gland, a tumor 2.5 by 1.5 by 1.0 cm. was found and removed. Histologic section disclosed a very vascular parathyroid adenoma composed chiefly of water-clear cells with small, irregular scatterings of "rose red" cells, scarcely any oxyphile cells. Along the margin of the capsule, a remnant of apparently normal parathyroid gland could be seen.

The postoperative course was uneventful. Associated with a fall in serum calcium to normal levels (but not below), the patient complained on the second postoperative day of tingling and numbness of the fingers and of some rigidity of the facial musculature. These symptoms responded readily to calcium administration. She was discharged October 16, 1936.

The patient improved in some respects after operation but the general result after eight months is unsatisfactory. She gained strength and some weight. The headaches disappeared. The pain in the arms vanished but recurred subsequently. The pains in both knees, hips and back are unimproved. These are clearly related to increased activities and are the result of faulty weight distribution due to flat feet and the persisting extreme deformity of the right tibia. Orthopedic measures have not helped. Osteotomy is contemplated.

Roentgen-rays three months after operation showed no change. The calcium and inorganic phosphorus contents of the serum have remained normal (table 2). The postoperative phosphatase activity of the serum, which is being followed with great interest, showed no definite decline six months after removal of the parathyroid tumor (table 2). Our typical cases of hyperparathyroidism exhibited some decrease in serum phosphatase activity within this period though they did not return to normal levels until after the lapse of at least a year.

Discussion. Case 1, A. G. The clinical, metabolic and many of the roentgenologic findings in this patient were characteristic of hyperparathyroidism. This diagnosis was established by demonstrating the presence of a typical parathyroid adenoma and by the characteristic postoperative

changes following removal of that tumor. The only atypical finding was the roentgen-ray demonstration of a condensation of bone, simulating Paget's disease, in the pelvis, associated with decalcification and cystic changes in the pelvis and elsewhere.



FIG. 1. Case A. G. (a) Pelvis, 1932, showing area of sclerosis with coarse trabeculations (simulating Paget's disease) in the left ilium, and cystic changes in the pubic bone and ischium. (b) Pelvis in 1935, showing more diffuse sclerosis with coarsely striated bone. (c) Pelvis in 1937, showing postoperative condensation of bone, indistinguishable from that seen pre-operatively.

Parts b and c of Figure 1 continued on pages 22 and 23

It is interesting to note that the sclerotic area present in the pelvis in 1932 (figure 1a) and in 1935 (figure 1b) is indistinguishable in character from the more extensive recalcification of the pelvis observed in postoperative films; and also from the postoperative appearance of recalcifying pelvic bones in some of our other typical cases of hyperparathyroidism. This resemblance suggests the possibility that the sclerosis of bone present in 1932



was not due to Paget's disease but to recalcification associated with an earlier, spontaneous remission of hyperparathyroidism—a transitory remission which preceded the exacerbation precipitating the symptoms that brought this patient to the hospital.

It is well known that patients with hyperparathyroidism may show distinct remissions and exacerbations in the course of the disease. In fact, complete spontaneous recovery has been described.^{4, 5, 10, 11} In such cases, recalcification following spontaneous recovery from hyperparathyroidism resulted in skeletal changes indistinguishable from those seen after surgical ablation of parathyroid tumors.

Ordinarily, the roentgenographic appearance of recalcifying bone, whether postoperative or spontaneous, could hardly be confused with Paget's disease. Cystic areas, particularly in the extremities, usually fill in to form a solid, structureless mass of sclerotic bone which shows none of the architecture characteristic of most Paget lesions. In the pelvis, however, as is evident from published cases and from our own postoperative observations, the resulting sclerosis may be more diffuse and the end-result may be difficult to distinguish from the sclerotic phase of Paget's disease.^{11, 12} Such changes have often been referred to in the literature as "pagetoid."¹¹ To call them Paget's disease,¹³ however, would seem at this time to be unjustified.^{1a, 7, 11, 12, 14, 15}



In summary then, case A. G. appears to be an instance of hyperparathyroidism simulating certain roentgenologic aspects of Paget's disease. The atypical, localized bone condensation simulating Paget's disease may well be the result of an earlier transitory, spontaneous remission in the course of hyperparathyroidism.

Case 2, M. B. Deformities typical of advanced hyperparathyroidism were associated in this patient with profound skeletal decalcification and numerous bone cysts, and with hypercalcemia and hypophosphatemia. The diagnosis of hyperparathyroidism was established by demonstrating the presence of a parathyroid adenoma. An apparently discrepant finding, however, was the enlargement of the skull with definite thickening and sclerosis of the cranial tables, superficially resembling that seen in some cases of Paget's disease.

The absence of "cotton-wool" lesions in the skull and of any increase in serum phosphatase activity * argue against the presence of Paget's disease in this patient. Expansion and sclerosis of the cranium have been described in many published cases of proved hyperparathyroidism (*vide infra*). We have ourselves seen similar skull changes develop postoperatively in healing

* The phosphatase activity of the serum is definitely increased in hyperparathyroidism too, ordinarily,* at least in cases with marked skeletal changes. It is possible that in this patient, destruction of bone was so extensive and of such long standing that bone repair was virtually at a stand-still. The atypical calcium balance is consistent with this possibility.

hyperparathyroidism. Such sclerotic transformation of the skull may well be due to recalcification occurring with remission in the course of hyperparathyroidism. In support of this interpretation, the calcium balance results were consistent with reduced or insignificant parathyroid over-activity at the time our studies were made.



FIG. 2. Case A. G., right tibia, showing decalcification and large cyst of the proximal half of the tibia, typical of hyperparathyroidism.

We regard case M. B., then, as an instance of advanced generalized *osteitis fibrosa cystica* with only moderately over-active parathyroid function when operated upon; and presenting spontaneous recalcification of the skull simulating Paget's disease superficially.

Case 3, L. L. In this instance, the roentgenograms were typical of *osteitis deformans*; the clinical symptoms and signs suggested Paget's disease but were not incompatible with hyperparathyroidism; and the blood analyses and markedly negative calcium balance due to loss of calcium in the



FIG. 3. Case M. B., right femur and proximal third of tibia. The deformities, extreme decalcification and multiple cyst formation are typical of advanced hyperparathyroidism.

urine clearly indicated parathyroid over-activity. The diagnosis of hyperparathyroidism was established by demonstrating the presence of a parathyroid tumor, such tumors not being found in patients with unequivocal and uncomplicated Paget's disease.¹⁶

Nevertheless, certain aspects of this case seem to us to be incompatible with the diagnosis of hyperparathyroidism. We could not find cases of hyperparathyroidism in the literature, nor have we seen any ourselves, with pre- or postoperative bone lesions comparable to those present in the right tibia of this patient (figure 5). The roentgenographic appearance of the tibia satisfies all the currently accepted criteria of typical *osteitis deformans*, and is indistinguishable from that of many patients in the large series of Paget's disease which we have had the opportunity to study.⁷ The appear-

ance of the skull, too, is characteristic of Paget's disease, though the skull mottling of hyperparathyroidism may be so coarse as to simulate this aspect of Paget's disease, particularly in some cases after operation. The presence of *osteoporosis circumscripta* of the skull (not to be confused with bone cysts occasionally found in the skull in hyperparathyroidism) provides further evidence for the interpretation of Paget's disease.¹⁷



FIG. 4. Case M. B., skull showing expansion and diffuse sclerosis of the cranial tables.

The postoperative course of this patient, unsatisfactory in many respects, likewise suggests the possibility of a bone lesion not due to hyperparathyroidism. And while the period of observation is yet too short, the persistently high postoperative level of serum phosphatase activity, despite the normal calcium and inorganic phosphorus content of the serum, is quite consistent with Paget's disease but contrary to what we have found in hyperparathyroidism.

The interpretation of this case which seems to us to do least violence to what is known about both diseases is that this is an instance of hyperparathyroidism associated with Paget's disease. Whether or not the presence of Paget's disease in this instance precipitated the development of hyperparathyroidism (or vice versa), is a matter of speculation. These possibilities cannot be ruled out. But in view of the evidence for the view that hyperparathyroidism and Paget's disease are discrete and unrelated entities, this seems unlikely.

The fortuitous co-existence of Paget's disease and hyperparathyroidism is not as improbable a coincidence as may appear. As is becoming in-

creasingly apparent, Paget's disease, far from being a rarity, is not uncommon, particularly at this patient's age period.⁷ Moreover, a critical examination of the literature shows that the number of cases which can



FIG. 5. Case L. L., right tibia, showing expansion with antero-lateral bowing, marked cortical thickening and coarse trabeculations consistent with Paget's disease.

really be regarded as presenting both hyperparathyroidism and Paget's disease is very small.

Cases in the Literature. The literature contains a number of cases presenting aspects suggestive of both hyperparathyroidism and Paget's disease. In many instances, however, particularly in the older literature, the mottling

of the skull now known to be typical of hyperparathyroidism was called "pagetoid" or confused with the "cotton-wool" appearance of Paget's disease. The skull changes in hyperparathyroidism may include definite expansion of the tables and when recalcification takes place, considerable sclerosis, either diffusely uniform or localized to one or more areas. Thickening of the skull, of marked degree in several instance,^{18, 19, and others} was

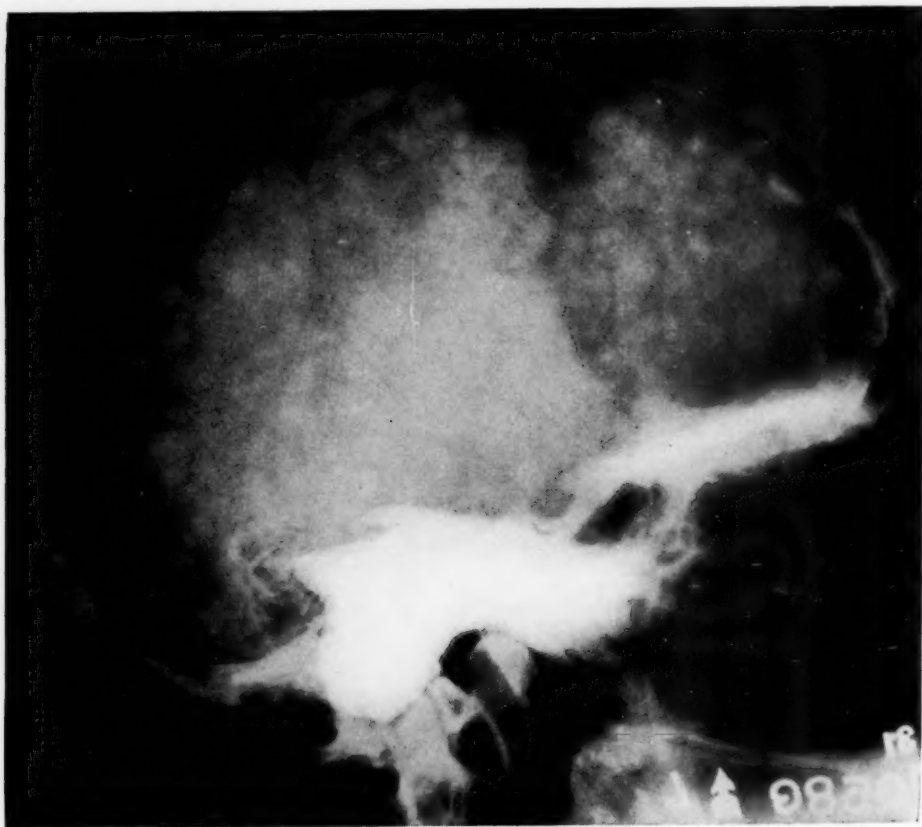


FIG. 6. Case L. L. The skull presents the typical "cotton-wool" appearance of Paget's disease.

described in 18 proved cases of hyperparathyroidism in the literature. The pelvis was the site of sclerotic bone lesions in several proved cases of hyperparathyroidism,^{1d, 20, 21, and others} as pointed out in connection with Case 1, A. G. Sclerotic areas have been found, further, in the vertebrae,^{22, 23, 24, and others} possibly due to compression fractures, and associated with healed fractures of the ribs. The bones of the extremities are more likely to show localized condensations of bone, obviously sclerosed cysts, but diffuse sclerosis, cortical thickening and coarsely striated trabeculae (accompanying severe deformities) have been described.^{25, 26, 11}

These areas of sclerosis did not resemble Paget's disease, for the most part, and were regarded usually as atypical manifestations of hyperparathyroidism. The observations of Kienböck and Markovits,¹¹ of Mandl¹⁵ and others suggest that the condensation of bone in many such instances is due to spontaneous recalcification occurring in the course of hyperparathyroidism.

Some cases interpreted as both hyperparathyroidism and Paget's disease would appear to be Paget's disease with cyst-like areas due to fatty degeneration of the bone marrow or to accumulations of osteoid tissue¹⁶; or Paget's disease with secondary decalcification such as is seen after prolonged immobilization. Other cases in this category are reported too briefly for evaluation.

There remain a few instances, such as Case 3, L. L., of this report, in which both hyperparathyroidism and Paget's disease appeared to be present. The coexistence of both diseases in these instances would appear to be fortuitous. An alternative explanation has been offered by Albright, Aub and Bauer^{1d}: If the unknown factor stimulating osteoclastic activity in Paget's disease is present in a patient in subthreshold degree, superimposed hyperparathyroidism, with its generalized stimulus to osteoclastic activity, may make the underlying disease become manifest.

Whatever the explanation for these cases, we feel justified in concluding that they do not seriously jeopardize the prevailing view that hyperparathyroidism and Paget's disease are distinct and unrelated entities. They serve, however, to emphasize two practical points: 1. Cases of hyperparathyroidism may present isolated areas of bone sclerosis; 2, appropriate chemical studies should be made even in cases of apparently obvious Paget's disease to exclude the possibility of hyperparathyroidism.

SUMMARY

1. Three proved cases of hyperparathyroidism are described, two presenting sclerotic lesions simulating Paget's disease, of the pelvis in one instance and of the skull in the other; and the third case apparently associated with Paget's disease of the tibia and skull.

2. A review of the literature shows that isolated areas of sclerotic bone may develop in hyperparathyroidism, particularly in the skull and pelvis. Most such areas resemble recalcification observed postoperatively and appear to be the result of spontaneous recalcification of the bones occurring in remission. Occasionally, the sclerotic bone lesions may simulate Paget's disease.

3. Cases of proved hyperparathyroidism associated with what appears to be typical Paget bone involvement have been described, but are very few in number. These few cases are thought to be not incompatible with the view that hyperparathyroidism and Paget's disease are distinct and unrelated entities.

BIBLIOGRAPHY

1. *a.* MICHAËLIS, L.: Ostitis deformans (Paget) und Ostitis fibrosa (von Recklinghausen), *Ergebn. d. Chir. u. Orthopädie*, 1933, xxvi, 381.
- b.* HUNTER, D., and TURNBULL, H. M.: Hyperparathyroidism: Generalized osteitis fibrosa, *Brit. Jr. Surg.*, 1931, xix, 203.
- c.* BAUER, W.: Hyperparathyroidism: A distinct disease entity, *Jr. Bone and Joint Surg.*, 1933, xv, 135.
- d.* ALBRIGHT, F., AUB, J. C., and BAUER, W.: Hyperparathyroidism, *Jr. Am. Med. Assoc.*, 1934, cii, 1276.
- e.* GUTMAN, A. B., SWENSON, P. C., and PARSONS, W. B.: The differential diagnosis of hyperparathyroidism, *Jr. Am. Med. Assoc.*, 1934, ciii, 87.
2. MANDL, F.: Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis fibrosa, *Arch. f. klin. Chir.*, 1926, cxliii, 1, 245.
3. CHRISTELLER, E.: Referat über die Osteodystrophia fibrosa, *Verhandl. d. deutsch. path. Gesellsch.*, 1926, xxi, 7.
4. WILICH, T.: Spontane Ausheilungsvorgänge bei generalisierter Osteodystrophia fibrosa, *Beitr. z. klin. Chir.*, 1929, cxlvi, 103.
5. MEYER-BORSTEL, H.: Über die Stellung der Recklinghausenschen zur Pagetschen Knochenkrankung, *Fortschr. a. d. Geb. d. Roentgenstrahlen*, 1930, xlii, 493.
6. GUTMAN, A. B.: The parathyroid glands, *Nelson Loose-Leaf Medicine*, 1935 revision, Thomas Nelson & Sons, New York.
7. GUTMAN, A. B., and KASABACH, H.: Paget's disease (osteitis deformans). Analysis of 116 cases, *Am. Jr. Med. Sci.*, 1936, cxcii, 361.
8. GUTMAN, A. B., TYSON, T. L., and GUTMAN, E. B.: Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of the bones, *Arch. Int. Med.*, 1936, lvii, 379.
9. GUTMAN, A. B., GUTMAN, E. B., and KASABACH, H. H.: Serum phosphatase activity in seventeen cases of osteoporosis circumscripta of the skull, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxiii, 295.
10. LINDÉN, O.: Case of osteitis fibrosa generalisata with well-marked tendency to spontaneous cure, *Acta radiol.*, 1934, xv, 202.
11. KIENBÖCK, R., and MARKOVITS, E.: Ein Fall von Ostitis fibrosa cystica generalisata, *Fortschr. a. d. Geb. d. Roentgenstrahlen*, 1930, xli, 904.
12. ASK-UPMARK, E.: Further observations on osteitis fibrosa generalisata, *Acta chir. Scandinav.*, 1931, lxviii, 551.
13. KIENBÖCK, R.: Über die Pagetsche Knochenkrankheit und Epithelkörperchentumoren, *Beitr. z. klin. Chir.*, 1934, clix, 597.
14. LIÈVRE, J. A.: L'ostéose parathyroïdienne et les ostéopathies chroniques, *Masson et Cie*, Paris, 1932.
15. MANDL, F.: Der Kalkstoffwechsel und seine Beziehungen zur Chirurgie der Epithelkörperchen, *Beitr. z. klin. Chir.*, 1935, clxii, 643.
16. SCHMORL, G.: Über Ostitis deformans Paget, *Virchow's Arch. f. path. Anat.*, 1932, cclxxxiii, 694.
17. KASABACH, H. H., and GUTMAN, A. B.: Osteoporosis circumscripta of the skull and Paget's disease. Fifteen new cases and a review of the literature, *Am. Jr. Roentgenol.*, 1937, xxxvii, 577.
18. SCHMORL, G.: Demonstrationen, *Verhandl. d. deutsch. path. Gesellsch.*, 1913, xvi, 352.
19. PENECKE, R.: Ueber zwei Fälle von Ostitis fibrosa Recklinghausen mit Epithelkörperchentumoren, *Verhandl. d. deutsch. path. Gesellsch.*, 1926, xxi, 97.
20. THOMASON, G., and SMITH, L.: Hyperparathyroidism, *West. Jr. Surg.*, 1933, xli, 78.
21. RIVEN, S. S., and MASON, M. F.: Adenoma of the parathyroid gland, with hyperparathyroidism, *ANN. INT. MED.*, 1936, ix, 1578.

22. HANKE, H.: Pathologische und theoretische Untersuchungen über Osteodystrophia fibrosa (von Recklinghausen) und ihre Beziehung zu Epithelkörperchentumor, *Arch. f. klin. Chir.*, 1932, clxxii, 366.
23. PINELLI, L.: Descrizione d'un caso presentante processi di osteodistrofia deformante del cranio e della colonna vertebrale e contemporane alter alterazioni di osteite fibrosa cistica degli arti, *Annali di radio. e fisica med.*, 1934, viii, 270.
24. LAHEY, F. H., and HAGGART, G. E.: Hyperparathyroidism, *Surg., Gynec. and Obst.*, 1935, lx, 1033.
25. HOFFHEINZ: Ueber Vergrößerungen der Epithelkörperchen bei Ostitis fibrosa und verwandten Krankheitsbildern, *Virchow's Arch. f. path. Anat.*, 1925, cclvi, 705.
26. SAINTON, P., and MILLOT, J. L.: Les lésions osseuses et parathyroidiennes dans la maladie de Recklinghausen, *Ann. d'anat. Path.*, 1931, viii, 70.

THE OXYGEN THERAPY OF PNEUMONIA

(FIVE YEARS' EXPERIENCE AT THE U. S. MARINE HOSPITAL,
NORFOLK, VIRGINIA) *

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THE use of oxygen as a therapeutic agent in pneumonia had its origin in the work of Haldane² and Meltzer.⁵ Among the earlier methods of administration was the face mask of Haldane and the hollow tongue compressor of Meltzer. Later, oxygen chambers were constructed at the Rockefeller Institute by Stadie and Binger, by Barach at the Presbyterian Hospital, New York, and by Boothby at the Mayo Clinic. It was not, however, until the introduction of bed tents, originally designed by Hill and modified by Roth, Binger, Barach and others, that it was possible to apply oxygen therapy to large groups of patients.

The physiological basis of oxygen therapy is well understood. The effect of anoxemia has been studied at high altitudes and experimentally in animals, in closed chambers from which oxygen has been partially exhausted. The symptoms of fatigue, cyanosis, nausea, delirium, and collapse have been observed in both instances. Stadie⁸ showed that there was a decreased oxygen saturation of the arterial blood in cyanosed pneumonia patients, and that the degree of under-saturation in these patients approached that found in severe mountain sickness. Meakins⁴ demonstrated that the cyanosis could be relieved, and the oxygen content of arterial blood returned to an approximately normal level by the inhalation of an oxygen mixture of sufficient concentration. In spite of these considerations, there is still considerable skepticism among clinicians as to the actual therapeutic value of oxygen in pneumonia. This skepticism is the result of the misuse or abuse of oxygen therapy. To a large extent, oxygen has been reserved for the seriously ill or almost moribund patients. The death rate among this group has naturally been very high. There are, as far as we know, no statistical data bearing on the routine adequate use of oxygen in pneumonia, nor a comparison of such a group with a control group of similar cases not so treated. It is our purpose, therefore, in this discussion, to offer certain figures bearing on the result of the early and adequate use of oxygen in pneumonia, and to present for comparison a similar group of cases in which oxygen was not used. A little over five years ago, oxygen therapy was first begun as a routine measure in the treatment of pneumonia patients at the U. S. Marine Hospital, Norfolk, Virginia, at the instigation of Surgeon S. L. Christian, Medical Officer in Charge, and carried out under the supervision of Surgeon W. L. Smith, United States Public Health Service.

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Since then it has been the rule to start oxygen on all cases of pneumonia as soon as the diagnosis is established, and to continue its use throughout the course of the disease, at a concentration of between 40 per cent and 60 per cent. Full credit should be given to the above mentioned officers for the adoption of this program in this hospital. So strong was their faith in the procedure that they seem to have converted the entire medical and nursing staff to their views on the subject.

Technic. The patient is made to understand that he will have to live beneath the tent during the entire duration of his disease, and that increased oxygen concentration is considered an important factor in his recovery. The oxygen tent is then placed over the patient, the flaps properly tucked under the mattress and the bed covers, and every effort made to prevent any possible leakage of air. It has been found by experience that with a good tight tent, 6 liters of oxygen per minute must be allowed to enter the tent, in order to maintain an oxygen content of 40 per cent to 60 per cent. This is thought by Barach to be the optimum concentration in the treatment of pneumonia. Frequent gasometric tests are necessary to ascertain the actual oxygen percentage. If the concentration is found below the optimal level, it is usually shown that a leaky tent needs adjustment.

Occasionally a greater supply of oxygen may be temporarily required. The proper level of temperature and moisture within the tent are automatically controlled by electric blowers that force circulation through a cooling dryer device containing cracked ice. Carbon dioxide is absorbed by its passage through a soda lime container.

The relatively high cost of continued oxygen therapy has deterred its more widespread adoption in the treatment of pneumonia. If, however, it can be demonstrated that its adequate use will result in the saving of lives, the cost factor becomes much less important.*

Statistics. In coöperation with a state wide study of pneumonia statistics, it became necessary to review the records of all pneumonia patients treated in this hospital for the last 10 years. This afforded an excellent opportunity for the evaluation of oxygen therapy in pneumonia. During the first four years of this period, oxygen was not employed. Its use was started in the spring of 1931. During the last five years, it has been a routine therapeutic measure, as outlined above. The figures for 1931, although favorable to oxygen therapy, were purposely omitted from the record, since the objection might be raised against them that the seasonal distribution influenced the good results. The total mortality of the 26 pneumonia patients during the year was approximately 21 per cent. The mortality without oxygen was 33.3 per cent, and that with oxygen 16.6 per cent.

* The cost of operating such an outfit on the above technic has been estimated at approximately \$5.00 a day. A tank of 220 cu. ft. of commercial oxygen at \$2.00 will last about 18 hours. Five pounds of soda lime at \$2.50 must be renewed every 24 to 36 hours. This frequent changing of soda lime renders the gasometric testing of carbon dioxide unnecessary.

The following tables show the comparative figures for the other years of the decade under study:

TABLE I
(A) Pneumonia Treated Without Oxygen *

	1927	1928	1929	1930	Total
Lobar pneumonia	13	11	12	13	49
Deaths	4	3	6	3	16
Percentage	30.8	27.3	50.0	23.1	32.65
Bronchopneumonia	10	5	11	12	38
Deaths	2	1	3	5	11
Percentage	20.0	20.0	27.3	41.7	28.95

(B) Pneumonia Treated With Oxygen *

	1932	1933	1934	1935	1936	Total
Lobar pneumonia	9	11	9	16	19	64
Deaths	1	3	1	4	3	12
Percentage	11.1	27.3	11.1	25.0	15.8	18.75
Bronchopneumonia	5	4	9	15	9	42
Deaths	1	1	2	1	2	7
Percentage	20.0	25.0	22.2	6.7	22.2	16.7

* All cases except terminal pneumonia.

TABLE II
Percentage Based on All Cases, Including Terminal Pneumonia

(A) Without oxygen 1927-1931	Mortality
Lobar pneumonia	42.1
Bronchopneumonia	34.1
(B) With oxygen 1932-1937	
Lobar pneumonia	31.9
Bronchopneumonia	29.0

TABLE III
Age Distribution

Age	(A) Without Oxygen (1927-1931)		(B) With Oxygen (1932-1937)	
	Cases	Deaths	Cases	Deaths
10-20	5	1	11	0
20-30	16	5	29	5
30-40	31	7	28	4
40-50	23	7	19	5
50-60	9	6	14	2
60-70	3	1	1	0
70-80	0	0	3	2
80-90	0	0	1	1

Experience with oxygen in two general hospitals in Norfolk, namely, Norfolk General Hospital and St. Vincent's Hospital, forms an interesting contrast with that embodied in the figures quoted above.

Table 6 includes all cases in these two hospitals on which accurate records of the amount of oxygen administered in the treatment of pneumonia are available.

TABLE IV
Racial Distribution

	(A) Without Oxygen (1927-1931)					
	White		Negro		Total White	Total Negro
	Lobar Pneumonia	Broncho-pneumonia	Lobar Pneumonia	Broncho-pneumonia		
Cases	32	26	17	12	58	29
Deaths	10	8	6	3	18	9
Percentage	31.25	30.6	35.3	25	31	31
	(B) With Oxygen (1932-1937)					
	White		Negro		Total White	Total Negro
	Lobar Pneumonia	Broncho-pneumonia	Lobar Pneumonia	Broncho-pneumonia		
Cases	39	28	26	13	67	39
Deaths	8	7	4	0	15	4
Percentage	20.5	25	15.4	0	22.4	10.25

TABLE V
Average Duration of Disease Before Admission

(A) Without Oxygen (1927-1931)		(B) With Oxygen (1932-1937)	
Lobar pneumonia	3.5 days	Lobar pneumonia	3.2 days
Bronchopneumonia	4.2 days	Bronchopneumonia	4.1 days

TABLE VI
All Pneumonias 1932-1937

Cases	Deaths	Recoveries	Percentage of Deaths
626	231	395	35.3
Cases Receiving Oxygen			
65	48	17	73.8
Oxygen—70 Hours or More			
9	3	6	33.3
Oxygen—30 Hours or Less			
37	32	5	86.5
Average Duration of Oxygen Therapy: 29.6 hours			

It is evident, from the figures in table 6, that oxygen therapy was reserved for the most desperate cases and was often a farewell gesture rather than a well conceived therapeutic effort. In only a small number of cases was oxygen given over a long enough time to be effective. It is to be noted that even in this group of severe cases, the death rate on the number receiving what might be termed adequate oxygen treatment (70 hours or more) was slightly less than the average death rate on all cases of pneumonia in these two hospitals. The report of Painton and Ulrich⁶ conforms closely to these figures. Of 149 patients receiving oxygen therapy on their service, 60 per cent died. It can readily be understood that with such experiences the average physician might assume that the use of oxygen in pneumonia is valueless.

SOCIAL AND ECONOMIC STATUS

Practically all of these patients treated at the U. S. Marine Hospital in both series came from the laboring classes. Most of them were merchant seamen, coast guardsmen, and civilian conservation corps boys. All but four were male. In nearly every case the clinical diagnosis was confirmed by roentgen-ray.

From the above data it is evident that the classes of patients treated with and without oxygen were similar in every respect. They received the same type of nursing and medical care in the same hospital with only one striking exception, namely oxygen therapy. A glance at the tables will suffice to show that there was an appreciable decline in mortality following the institution of this therapeutic measure. Serum therapy did not enter into the picture, since only one patient received this treatment. He was a Type I pneumonia patient in the 1936 group, who was given 110,000 units of Felton Type I serum, and recovered.

Comments. It is a fact that anoxemia, a reduction of oxygen in the arterial blood, occurs to some extent in every case of pneumonia. When this is sufficiently marked it will manifest itself by cyanosis. That anoxemia is a harmful condition is at present recognized by all. Barach expresses it well when he sums up its effects as follows: "In summary, it might well be said that the disturbance of the gastrointestinal system is manifested by nausea, vomiting and diarrhea; the respiratory system by increased rate and depth of respiration or by periodic respiration, and later by rapid shallow respiration; the circulatory system by a constant and progressive increase in pulse rate, and in the end by a fall in diastolic pressure and cardiac failure; the central nervous system by headache, visual disturbances, irrational states and delirium, and finally, by coma and death." Hence the appearance of any of these symptoms in pneumonia may be attributable to a certain degree to anoxemia.

In combating anoxemia, by increasing the oxygen of the circulating blood, oxygen therapy acts not only locally in the lungs but throughout the body. Oxygen is a need of all the tissues, and the proper function of all the

organs depends upon its adequate supply through the circulating blood. This is the reason that in order to be most efficacious in pneumonia, oxygen administration must be begun early in proper concentration and continued throughout the course of the disease.

It is our opinion that the prevention of cyanosis rather than the treatment of cyanosis after it has developed is the important objective. A severe degree of anoxemia may lead to irreversible degenerative changes.

Beneficial Effect of Oxygen. It has been claimed that the beneficial effects of oxygen in pneumonia are manifested in various ways. These have been listed by different authors as follows:

- (1) A disappearance of cyanosis.
- (2) A reduction of the respiratory rate.
- (3) A diminution of the heart beats.
- (4) A lowering of the body temperature.
- (5) A lessening of the harassing cough.
- (6) An elevation of the blood pressure.
- (7) A prolongation of life allowing more time for the development of the immunization phenomena.

In our experience it seems difficult to substantiate all of these claims. An actual lowering of the temperature, pulse, and respiration curve cannot usually be demonstrated on the patient's chart. The course of the disease is not shortened. What has been observed is that the patient becomes quieter, breathes easier, and will often fall into a restful sleep following oxygen inhalation. Cyanosis and delirium are lessened, and the general condition and comfort of the patient seem distinctly improved. It is frequently noted that the patient requests that he be placed under the oxygen tent again, when it has temporarily been removed.

Recent Developments. Because of the high cost of soda lime, the discontinuance of its use has recently been advised. Rosenbluth shows that a supply of oxygen, at 6 liters per minute, will permit the carbon dioxide to accumulate only up to 4 per cent within a properly closed tent, if soda lime is not used to absorb it. By increasing the inflow of oxygen to 8 to 10 liters per minute, the carbon dioxide will not rise above 1.5 per cent which is well within the limits of safety. He believes that an atmosphere containing even 2 to 4 per cent of carbon dioxide is not detrimental to the patient. From the above it is evident that the soda lime can be dispensed with and at a little saving. Some of the newer oxygen tents on the market are built upon this principle. There is an additional advantage in the increased oxygen allowance, in that it permits the nurse greater freedom in handling the patient. The avoidance of slight leaks becomes relatively less important.

Henderson³ advocates the addition of carbon dioxide to oxygen (his carbogen) in the treatment of pneumonia. He believes that a concentration of 4.5 to 5 per cent of carbon dioxide is definitely beneficial. He states:

"The results reported indicate, and more recent extensive unpublished experience confirms, that inhalation of carbogen (5 per cent carbon dioxide in 95 per cent oxygen) affords the same benefit in overcoming cyanosis as does oxygen and has the additional advantage of inducing also a deeper and often slower rate of breathing." These claims of Henderson have, however, not been confirmed.

The danger of the inhalation of too high a percentage of oxygen upon the parenchyma of the lungs which was formerly so strongly stressed seems, perhaps, to have been exaggerated. Evans and Durshordwe¹ demonstrate that even at nearly a 100 per cent concentration, oxygen does not seem to irritate the pulmonary tissues.

In view of these recent developments, it is proposed to modify the present technic of oxygen tent operation in this hospital. In the future, the oxygen flow will be adjusted at 10 liters per minute, and the soda lime will be discarded. The results of this new phase of oxygen therapy, and whether the present good record can be still further improved, will remain for the future to decide.

CONCLUSION

(1) In our experience a very definite lowering of mortality in both lobar and bronchial pneumonia has been observed since the institution of routine oxygen therapy at the U. S. Marine Hospital in Norfolk.

(2) In order to obtain optimal results in pneumonia, oxygen therapy should be started early and should be continued in adequate concentration throughout the course of the disease.

REFERENCES

1. EVANS, J. H., and DURSHORDWE, C. J.: Further observation on oxygen therapy in the treatment of pneumonia, *Current Researches in Anesthesia and Analgesia*, 1932, xi, 193.
2. HALDANE, J. S.: The symptoms, causes and prevention of anoxemia, *Brit. Med. Jr.*, 1919, ii, 65.
3. HENDERSON, YANDELL: Reasons for the use of carbon dioxide with oxygen in the treatment of pneumonia, *New England Jr. Med.*, 1932, ccvi, 151.
4. MEAKINS, J. C.: Therapeutic value of oxygen in pulmonary lesions, *Brit. Med. Jr.*, 1920, i, 324.
5. MELTZER, P. J.: The therapeutic value of oral rhythmic insufflation of oxygen, *Jr. Am. Med. Assoc.*, 1917, lxix, 1150.
6. PAINTON, F. J., and ULRICH, H. J.: Lobar pneumonia: an analysis of 1298 cases, *ANN. INT. MED.*, 1937, x, 1345.
7. ROSENBLUTH, M. B., and BLOOM, M.: Oxygen therapy, *Jr. Am. Med. Assoc.*, 1932, xcvi, 396.
8. STADIE, W. C.: The oxygen of the arterial and venous blood in pneumonia and its relation to cyanosis, *Jr. Exper. Med.*, 1919, xxx, 215.

SECONDARY AMYLOIDOSIS: RESULTS OF THERAPY WITH DESICCATED WHOLE LIVER POWDER*

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AMYLOIDOSIS secondary to a chronic infection is a complication of serious prognostic significance. In human beings presenting clinical signs of amyloidosis, the condition usually progresses to a fatal termination because the underlying cause remains active. Very few reported cases of recovery appear in the literature.¹⁻¹³ The majority of these recover only after an extensive operation which eradicates the primary disease provided the operative procedure is carried out early. This method of treatment can be employed with success only in a limited number of instances. The treatment of secondary amyloidosis in the majority of patients is therefore directed towards mitigating the primary illness through general measures. The results hitherto have been wholly unsatisfactory. Prior to the institution of the therapy which will be described later, all our patients died within two years.¹⁴

Several years ago, we observed clinical evidence of the disappearance of amyloid in human beings even in the presence of active tuberculous sup-
puration of bone following the administration of a powdered whole liver preparation. Brief mention of this was made at that time.^{8, 15, 16} However, we have felt the need for further clinical observation and investigation, as well as a more extended experimental study. This caused us to delay the present report. Our original observations have now the support of well controlled laboratory studies. In the meantime, a preliminary report of our early results was made by Whitbeck.⁹ It is over eight years now since the institution of this therapy at Neponsit Beach Hospital for Children. Our clinical success with this material which has been substantiated by our experimental work^{15, 16} and confirmed⁴² by others, warrants a more detailed presentation of our results.

The diagnosis of amyloidosis was made in each case after a period of observation and study of at least four to six months. All subjects had a primary suppurative disease of long standing and showed classical symptoms of amyloidosis consisting of waxy pallor, loss of weight, emaciation, weakness, large abdomen with dilated and tortuous superficial abdominal veins, marked and progressive hepatomegaly and splenomegaly, albuminuria and casts of every description, and positive Congo Red test giving 100 per cent withdrawal of intravenously introduced dye.

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After it was definitely established that amyloidosis was present and after a minimum period of six months had elapsed during which time it was observed that the lardaceous condition was progressing unfavorably, liver therapy was instituted in selected cases. The treatment consisted of the administration of a desiccated powdered whole liver preparation in doses of 4 to 8 grams three times a day.*

It was given in a suitable vehicle such as fruit juices, cereal, milk, jelly or jam. In addition to the liver therapy, the usual general hygienic and medical measures were carried out such as an adequate diet, fresh air, sunlight, heliotherapy, daily salt water baths and dressing, and some form of orthopedic non-surgical immobilization. These latter measures differed in no wise from similar measures employed in each case before liver therapy was instituted.

CASE REPORTS

Case 1. J. G., male white child, 8 years old on admission, entered Neponsit Beach Hospital for Children on May 29, 1923. He had tuberculous disease of the second, third and fourth lumbar vertebrae. There were two discharging sinuses, one in the left gluteal region and one in the left iliac region just to the inner side of the left anterior superior spine. By January 16, 1924, the sinuses had closed and were apparently healed; and on March 24, 1924, a plaster jacket was applied. He was allowed out of bed for short periods of time, but on March 20, 1925, the sinuses re-opened and commenced to discharge. The temperature was elevated, reaching 104° F.

The unfavorable condition persisted. The child displayed a poor appetite, lost weight and became increasingly paler. By July 1926, definite amyloidosis may be said to have set in. The liver and spleen were 2.5 and 1.3 cm. respectively below their corresponding costal borders in the mid-clavicular line.† The child's condition declined progressively so that by April 14, 1929 his state was critical. He was very emaciated and pale, and had several attacks of epistaxis, hematemesis and melena. There was generalized anasarca including hydrothorax and ascites. The liver edge was below the crest of the ilium and the spleen was down 11.5 cm. At this time whole powdered liver was given in doses of 4 gm. three times daily and within one month increased to 8 gm. three times daily.

Within six months after the administration of the liver therapy there was striking improvement in the patient's general appearance and in his clinical symptoms. Although the temperature was still moderately elevated, and the sinuses continued to discharge freely, the generalized anasarca had completely disappeared; the superficial abdominal veins were much less prominent and the liver and spleen were 5 cm. and 3 cm. respectively. The subsequent course was favorable. After one year of treatment and in spite of the persistence of signs of activity as evidenced by the presence of fever, discharging sinuses and progressive destruction in the bones seen in the roentgenograms, the liver was 2.5 cm. and the spleen was just palpable. Albuminuria was still marked. Two and one half years of therapy resulted in the

* The whole liver powder is one that must be prepared under certain specific conditions so that in the process of desiccation, the chemically unknown principle is not destroyed or reduced in its potency. Briefly, we would consider a suitable method of preparation one which consists of removing extraneous material from the liver, chopping up the livers and drying them in vacuum. The temperature should not be above 35° F., preferably below this level.

† In succeeding enumerations of the size of the liver and spleen, mention will be made only in terms of centimeters, it being understood that such measurements are made in the mid-clavicular line below their costal margins.

complete recession of the liver and spleen so that they were no longer palpable. At approximately this period the sinuses closed and have remained healed up to the present. To date, after a period of nearly eight years, the child has remained clinically well and is quite active. Congo red test showed 100 per cent withdrawal of the dye in April 1929 and again in July 1931.

Case 2. C. I., male white child, 7½ years on September 8, 1924, the date of admission to Neponsit Beach Hospital for Children. About three months prior to admission, there developed pain and swelling of the right knee associated with fever. The condition became progressively worse so that on admission, the child was pale and emaciated and presented a marked fusiform swelling of the right knee with several discharging sinuses.

High temperature with discharging sinuses, loss of weight, increasing anemia and albuminuria continued and by January 1927, the abdomen was large and the liver and spleen were 5.2 cm. and 2.6 cm. respectively. By February 1928, the swelling of the knee was tremendous with profuse discharge from several sinuses. The liver was 10.4 cm. and the spleen 5 cm. The abdomen was very prominent with marked dilatation of the superficial abdominal veins. The urine boiled solid with albumin; the Congo Red test was positive. At this time liver therapy in doses of 4 to 8 gm. three times daily was instituted.

Although the temperature was elevated and the sinuses continued to discharge up to August 1930, the child's condition showed very early striking improvement. After six months of therapy the liver was 5.5 cm. and the spleen 2.8 cm.; and after 2½ years (February 1930) the liver and spleen were no longer palpable. However, the Congo Red test on July 1930 still showed complete withdrawal of the dye. At the time of discharge from Neponsit Beach Hospital (August 6, 1930), to another institution, all clinical signs of amyloidosis were absent. Up to the present, six and one half years after discharge from the hospital and nine years after the institution of liver therapy, there have been no recurrences of any symptoms or signs referable to amyloid disease. Liver therapy was discontinued upon his discharge from the hospital in 1930.

Case 3. E. A., male white child admitted to Neponsit Beach Hospital for Children on October 6, 1925, at the age of four years. About eight months prior to admission a diagnosis of tuberculous infection of the lumbar vertebrae was made. Fusion of the involved vertebrae by bone graft was performed at another institution. Shortly thereafter suppuration appeared in the region of the left flank and near the left anterior superior spine. The former was incised, drained and the wound sewed up. The incision soon again discharged spontaneously and continued to drain. At this stage the child was transferred to Neponsit Beach Hospital for Children.

On admission the child was in fair condition and presented a sinus in the left iliac region which discharged moderately. The condition remained unchanged until 14 months later when elevation of temperature set in associated with swelling in the right gluteal region just behind the greater trochanter of the femur. An abscess which formed was opened and drained. After discharging for a short time, it finally healed. This was followed by the formation of another abscess on the posterior surface of the right thigh, which was incised and drained.

From this point on, the temperature continued to be elevated at varying levels and the discharge from the several sinuses persisted. The child's condition became worse. Loss of weight, pallor and progressive enlargement of the abdomen, liver and spleen became apparent about two years after admission to Neponsit Beach Hospital. On August 9, 1929, when the liver was 12.8 cm. and the spleen 6 cm., liver therapy was instituted. At first there was no definite improvement in his general appearance and condition. Within six months the liver was 9 cm. and the spleen 3.5 cm. At nine months the liver edge was at 7.7 cm. and the splenic margin at 2.8 cm. However, he took the liver therapy very poorly because of its unpleasant taste and

soon began to take it very irregularly, often refusing it for periods of two months. Nausea and vomiting were the chief symptoms accounting for his inability to tolerate the medication. Shortly before death which occurred on January 14, 1931, pre-uremic symptoms set in. He lapsed into a stuporous state, displaying occasional twitchings and minor convulsive seizures.

Case 4. R. H., male colored child, about seven years of age, entered Neponsit Beach Hospital for Children on July 8, 1927, with Pott's disease of approximately one year's duration. Upon admission he presented an extensive kyphosis involving the fourth dorsal to the second lumbar vertebrae with a discharging sinus in the right groin at the inner side of the anterior superior spine. In addition he had chronic pan-uveitis of the right eye showing corneal and iritic opacity. There was amaurosis of the right eye. The chest was barrel shaped. The abdomen was prominent and the liver and spleen were each about 1.3 cm.

The child had an active tuberculous infection which varied in its severity from mild to moderate. The temperature ranged between 100 and 101° F. with occasional bouts of temperature from 102° to 103° F. The sinus in the right groin continued to drain moderately. The abdomen became progressively larger, displaying increasing dilatation of the superficial veins and enlargement of the liver and spleen. He had recurring attacks of epistaxis, edema, ascites and acquired frequent respiratory infections. By November 1929, his condition was markedly worse. The liver was down to the crest of the ilium and the spleen was 5 cm. Liver therapy was instituted but it apparently did not alter the downward course of the child. He died June 20, 1930. The entire duration of his illness, from the first symptoms of the primary disease, was about four years.

Case 5. M. N., male white child, eight years of age, was admitted to Neponsit Beach Hospital on July 9, 1926. About 3½ years before, following a fall, his knee was injured and became swollen and red; but there was no complaint of pain in the hip at that time. This condition subsided and disappeared. About five months prior to admission, the boy experienced pain in the right hip with other attendant symptoms of joint involvement. At the time of entrance into the hospital, there was a large abscess on the outer side of the right thigh in the upper third. This was incised and drained; and the wound was closed. Shortly thereafter progressively increasing discharge from the wound was observed. From this time on, elevation of temperature, profuse discharge from several sinuses, anorexia, loss of weight and increasing pallor were constant symptoms. By September 1927 it was evident that the child had amyloidosis. On February 29, 1928, the liver was 8 cm. and the spleen 5.5 cm. On the latter date, liver therapy in doses of 4 gm. three times daily was given, the dose later being increased to 8 gm. thrice daily. On August 2, 1928, the bone infection was still active, but there was evident improvement in his general appearance and color. He gained in weight (11 lbs.). No ascites was observed. His liver and spleen were 4 cm. and 1.5 cm. respectively. Roentgenograms of his extremities, however, still showed progressive destruction of the head of the femur and adjacent portion of the neck and considerable involvement of the acetabulum and ilium. On May 20, 1929, his condition was satisfactory but there was still moderate discharge from numerous sinuses. Both the liver and the spleen were no longer palpable.

He continued to improve although fever and discharge from the sinuses persisted. On May 2, 1930 erysipelas set in. The course was stormy and the infection of the hip became aggravated. By January 1931, the liver was again 5 cm. and the spleen 3 cm. Within three months under continued liver therapy the liver and spleen again receded to 3.8 and 1.2 cm. However, a recrudescence of his primary disease set in and the amyloidosis advanced. In September 1931, the liver was 7.7 cm. and the spleen 5.2 cm. Shortly after this period, the parents insisted on taking him home. He was discharged against medical advice on September 28, 1931. At home he re-

ceived no liver therapy and his condition became progressively worse. He died about eight months after leaving the hospital.

Case 6. S.B., male white child, 7½ years of age, admitted to Neponsit Beach Hospital for Children on May 14, 1926. About nine months prior to admission he developed a staphylococcal infection of his hand which was operated upon. Shortly thereafter he complained of pain in the right hip. He was operated upon and the hip region drained, at another institution where he resided for five months.

On admission he presented an active infection of his right hip with several discharging sinuses. This together with moderate elevation of temperature continued and by May 1928, he presented definite signs of amyloidosis. Roentgen-ray showed extensive destruction of hip joint, acetabulum, pubic bone and, in fact, almost the entire right ilium. There was marked rarefaction of the head, neck, trochanter and shaft of the femur. In February 1930, there set in an infection of the left shoulder and shortly thereafter suppuration and sinus formation ensued.

The child's condition became progressively worse. The temperature ranged between 101 and 103°; the infections in the right hip and left shoulder continued to be active and to present discharging sinuses. By July 1930, the amyloidosis was moderately advanced. The liver was 8 cm., the spleen 3.5 cm. At this time, liver therapy was instituted. Within six months there was evident improvement in his physical condition. Although the infection was still actively present in his bone, the temperature continuing to be moderately elevated and the sinuses persisting, the liver was reduced to 4.5 cm. and the spleen to 2 cm. Fourteen months of liver treatment (July 1930 to September 1931) resulted in complete disappearance of both organs below their respective costal margins. However, the temperature still fluctuated between 99° and 101° F. and there was still slight discharge from all sinuses. Roentgen-ray still showed activity of the tuberculous process in the bones but revealed some improvement in the appearance of several of the bones, particularly the ilium.

Liver therapy was continued and by April 27, 1932, the temperature was normal, the sinuses were healed and the bone lesions were inactive. However, the child continued to show a marked albuminuria with numerous leukocytes and many erythrocytes for several years. Complete urological examination failed to show any evidence of infection, or any other involvement of the urinary tract. The child was last seen in December 1936 when it was observed that his general physical condition was excellent; his bone condition had remained apparently healed but his urine still showed moderate albuminuria with many leukocytes and few erythrocytes. The liver and spleen could not be felt; there were no signs or symptoms to suggest amyloid disease.

Case 7. E. L., male, colored child, 4½ years of age, admitted to Neponsit Beach Hospital on October 19, 1928. About two years before, following an injury, tuberculous osteomyelitis of the lower left femur and upper left tibia set in. He was at another institution during this time. On admission he displayed eight moderately discharging sinuses about the left knee joint. The latter was markedly swollen presenting a typical fusiform appearance. The abdomen was prominent with dilated superficial veins; liver was 9 cm. and spleen 4.5 cm.

The temperature was elevated, rising at times to 104° F. and the sinuses continued to discharge freely. By February 1929, the child's condition was very poor. He was markedly emaciated and presented marked pallor of the mucous membranes of lips, conjunctivae and finger nails. The liver was 11.5 cm. and the spleen 6 cm. His abdomen was distended with fluid. At this time, liver therapy was started in doses of 4 to 8 gm. three times daily. With treatment the child showed initially a very significant improvement with reduction in the size of the abdomen, liver and spleen and the disappearance of ascites. On February 7, 1930, one year after therapy had been begun, the abdomen was slightly prominent with no dilatation of the superficial abdominal veins. The liver was 2 cm., the spleen barely palpable. However,

temperature and discharge from all sinuses still continued. Roentgen-ray showed continuing activity, revealing moderate destruction of the outer condyle of the femur, and upper end of the tibia, involving the epiphyseal line and the diaphysis of the femur. One and one-half years later, the temperature became normal and there were only three discharging sinuses; the liver was just palpable. Roentgen-ray showed considerable destruction of the lower end of the femur and the epiphysis on the outer half, and moderate destruction of the epiphysis of the tibia. The patella was indistinct and irregular in outline. Two years later (February 1930), the liver and spleen were no longer palpable and all sinuses except one had healed. There now occurred a steady and definite diminution in the amount of thickening and swelling about the knee. Three and one half years after therapy had been instituted, the roentgenograms began to show healing in the knee joint. The child continued to improve and by August 13, 1934, 5½ years after the onset of the disease, and 4½ years after institution of liver therapy, the last sinus closed and remained healed.

Case 8. M. M., female, white child, 8½ years of age, was admitted to the Neponsit Beach Hospital on August 14, 1929 with the history that about one year before, she struck her left thigh against an iron bar. This was followed a few days later by elevation of temperature and severe pain in the left hip. She was admitted to another institution where she was operated upon for osteomyelitis of the left femur. For about a month after the operation, the child's condition seemed to improve. At the end of this period elevation of temperature and pain in the right upper thigh recurred. A plaster spica was applied, but suppuration and spontaneous discharge from the involved area occurred shortly thereafter. Blood cultures taken with significant pyrexia always showed abundant colonies of *Staphylococcus albus*.

The child was admitted to Neponsit Beach Hospital in very poor condition. She was thin and pale. In the region of the great trochanter on the left side, there were two discharging sinuses, and three sinuses were present near the trochanter on the anterior surface of the right thigh. During her residence in the hospital, the child displayed a relapsing course. At irregular periods, a new focus of infection arose, or a previous one became active. On each occasion, fever of varying degree, pallor, loss of weight, prostration, anorexia, etc. were manifested. The infection either subsided spontaneously in the course of time or progressed to local suppuration. Blood cultures taken on several of these occurrences were positive for *Staphylococcus albus*. Several blood transfusions were administered.

With repetitions of the active infections the child became progressively worse. By May 1930, definite amyloidosis may be said to have set in. By January 1931, the child was markedly pale and emaciated with abdominal enlargement and dilated superficial abdominal veins. The spleen and liver were enlarged to 5.5 cm. and 8 cm. respectively. On January 14, 1931, liver therapy was instituted.

Although the child's infection continued to be of a relapsing nature, with liver treatment the child showed definite improvement of her amyloidosis. After one year of therapy, she had gained seven and one-half pounds and the spleen was 2.0 cm., the liver 3.8 cm. No ascites was present. Two years of therapy resulted in decrease of the size of the liver to 1.5 cm. and of the spleen to the point where it was barely palpable. Within three years, there was no objective evidence of amyloidosis except for such symptoms as pallor and albuminuria. The chronic osteomyelitis, however, continued to be active and the child was transferred to another institution on December 3, 1934 in order to obtain surgical treatment. At the latter institution an extensive operation was performed. After an irregular course the bone infection subsided and has remained inactive to date.

Case 9. F. S., female white child, aged 5 years, admitted to Neponsit Beach Hospital on September 11, 1929 because of tuberculosis of the left hip, the onset of which had occurred on November 14, 1927. She was treated by immobilization in a cast. About one month prior to admission gross suppuration set in. This was in-

cised and drained. On admission the child was thin, pale, and displayed a very active destructive tuberculous infection of the left hip with several discharging sinuses.

Since her admission, the temperature had constantly been elevated, ranging usually between 101 and 102°, but often rising to heights of 103 to 104° F.; the sinuses continued to discharge freely and two new areas of suppuration developed. Roentgen-ray on January 8, 1931 showed considerable destruction of the acetabulum and head and adjacent portion of the neck of the left femur. The first evidence of amyloidosis was noted by May 1930. On January 20, 1931 when liver therapy was instituted the abdomen was very prominent. The liver and spleen were both 3 cm. Within 1½ years there occurred such complete recession of the liver and spleen that each organ was no longer palpable.

The child's infection, however, continued to run an active course with persistence of discharging sinuses, fever and symptoms in the left hip joint. Anorexia, loss of weight, weakness and pallor continued. On June 1, 1934 the liver and spleen again began to enlarge. The liver was 1.5 cm., the spleen barely palpable. On October 22, 1935, the liver was 5.5 cm., the spleen 4 cm. Persistence in administering liver therapy led eventually to recovery so that, in spite of the continuing active infection, by July 10, 1936, the liver had receded to 2.5 cm., and the spleen to 1.5 cm. On October 15, 1936, the liver was 2 cm. and the spleen was just palpable. Liver therapy was discontinued for two months (October 15 to December 11, 1936) and it was observed that her liver increased to 7 cm. and the spleen to 2 cm. The liver product was therefore resumed again resulting in striking reduction in the size of both organs to 2.5 cm. and 1.5 cm. respectively. The status of the tuberculous infection had not varied in its severity during these latter periods.

Case 10. T. F., male, white child, 8 years of age, admitted to Neponsit Beach Hospital on June 3, 1932, with the diagnosis of tuberculosis of the left hip of about four years' duration. On January 25, 1932, an extra-articular fusion of the left hip was performed at another institution. On April 26, 1932 the temperature rose to 104° F.; the wound began to discharge.

On admission the child appeared pale and was poorly nourished and developed. He presented a large granulating T-shaped wound over the left hip and ilium. It was noted that the abdomen was distended but the liver and spleen were not palpable.

Temperature continued to run as high as 102° F. nearly every afternoon. On October 24, 1932, the roentgen-ray showed extensive destruction about the head of the left femur and acetabulum. The liver and spleen were now both palpable. With continuance of the moderate pyrexia and active infection about the left hip, including profuse discharge from the sinuses, the abdomen, liver and spleen increased progressively in size. On March 3, 1933, he was markedly emaciated and pale, the liver and spleen were each 5 cm. Liver therapy was then instituted.

The tuberculous infection continued to be very active. Six months after liver treatment (September 15, 1933) had been started, the liver had increased to 7.5 cm. although the spleen remained at 5 cm. Roentgen-ray showed a more extensive involvement and destruction of the left acetabulum, femur and ilium. One year of therapy resulted in a definite improvement in the amyloidosis in spite of the active hip infection. The liver and spleen were each 2.5 cm. The temperature continued to be elevated and the sinuses to drain profusely. By August 1934 or about 1½ years later, the liver had enlarged to 5 cm. and abdominal ascites was present. Persistence of liver therapy led to slow but steady improvement. In spite of the relapsing nature of his primary infection, two years later on March 5, 1935, the waxy pallor, enlargement of the abdomen, prominence of the superficial abdominal veins, etc. were absent. The liver, however, was 4 cm. and the spleen 1.5 cm. There was no ascites. One year later, in March 1936, the liver was 2.5 cm., the spleen 1 cm. Temperature now ranged between 100° and 101° F. and discharge from the sinuses was less. Liver therapy was discontinued in July 1936 when both

organs were just palpable. On October 15, 1936, there was slight discharge from the sinuses about the left hip. The liver and spleen were no longer palpable. Examination on February 11, 1937 revealed no objective evidence of amyloidosis.

Case 11. E. Z., male white child, aged 10 years, admitted to Neponsit Beach Hospital for Children on July 15, 1930. Three years before the child had injured his right lower extremity. A nurse noticed the child limping on the street and induced the mother to bring the child to a hospital for treatment. On May 31, 1930, the child was examined at a hospital where extensive destructive disease of the right hip was noted. Stretching was done preliminary to an extra-articular fusion. The latter was performed on June 30, 1930.

Child was admitted in very poor condition, thin and looking pale. The abdomen was not prominent, the liver and spleen not palpable. Urine examination was negative. In the hospital the temperature was moderately elevated, and there was considerable discharge from two sinuses. On January 9, 1931, definite signs of amyloidosis were observed. The liver and spleen were each 1 cm. Roentgen-ray showed marked destruction of the femoral head and acetabulum. The condition became progressively worse so that by September 11, 1931, the signs of amyloidosis were advanced. The child presented a striking waxy pallor and was very emaciated. The abdomen was markedly distended with fluid; both legs and feet were edematous. The liver was 5.3 cm., the spleen 3 cm. Roentgen-ray showed increased destruction in the region of the acetabulum. Liver therapy was instituted. The amyloid condition continued unchanged except for the disappearance of the edema of the lower extremities and a significant decrease in the ascites. On January 19, 1932, there was marked thickening and enlargement of the right hip with a reddened area and slight fluctuation over the right ilium. The size of the liver and the spleen had diminished to 4 cm. The incitant tuberculosis continued very active.

With slight fluctuations in the course, the status of the amyloidosis remained unchanged until July 1934 or about three years after the institution of treatment. Although the temperature was still elevated, the sinuses continued to discharge profusely, and roentgenograms showed increasing involvement of the right ilium and moderate involvement of the head and neck of the femur, the enlargement of the abdomen was now only moderate and the liver and spleen were 5 cm. and 1.5 cm. respectively. For the next year and one half (or until January 1936) the child's symptoms and roentgenologic findings remained unchanged. On the latter date, the liver was 4 cm., the spleen 1.3 cm. Roentgen-ray showed now marked destruction of part of the right ilium, upper end of the femur, pubis and ischium with considerable distortion of the pelvis. What remained of the neck of the femur was still in the acetabulum; marked adduction and flexion were present. The active symptoms of the primary infection continued unabated. The condition of the amyloidosis, particularly in the liver and spleen, varied. In July 1936, after five years of treatment, the liver was 3 cm., the spleen 1.3 cm. Liver therapy was discontinued on the latter date to note the effect of such a procedure. On October 10, 1936 the liver and spleen were 6 cm. and 1.5 cm. respectively. Liver treatment was resumed and on January 26, 1937 the patient's liver was 4 cm., his spleen 1.5 cm. Moderate discharge from the sinuses and temperature elevation were still present. On May 21, 1937, both the liver and spleen were just palpable. All other signs of amyloidosis were absent.

Case 12. V. C., male colored child, 10 years of age, admitted to Neponsit Beach Hospital on May 12, 1934. Following an injury in March 1933, the child experienced pain in the right sacroiliac joint. About one month later, a soft fluctuant mass developed and was aspirated. A plaster spica was applied giving the patient comfort for a time. Soon, however, the abscess again broke down; roentgenograms and guinea pig tests at this time were positive for tuberculosis. The child continued to run a spiking temperature. The plaster was changed at intervals of 8 to 10 weeks.

On admission the child appeared emaciated, pale, with a prominent abdomen and a liver and spleen that were just palpable. There was a huge granulating area over the right great trochanter four inches square, bathed in pus. There was also one of similar size near the crest of the right ilium and in the right groin there was a profusely draining sinus.

The temperature was irregular and remittent. The patient's condition became rapidly worse. Roentgenograms showed marked rarefaction of all the bones of the right femur and ilium. On November 30, 1934, the liver was 3 cm., the spleen 1.5 cm. Liver therapy was instituted at this juncture. During the first three months of treatment there was slight improvement in his physical appearance. With the continuance of the severity of his primary condition and his inability regularly to take the liver preparation without vomiting, his condition became worse. On November 1935, the liver and spleen were 8 cm. and 5 cm. respectively. However, he showed irregular periods of improvement in the amyloid condition, each lasting one to three months. His tuberculous infection continued unabated. In May 1936 after about 1½ years of inconstant liver treatment, the abdomen became very prominent and marked ascites set in. In addition the liver and spleen had increased to 9 cm. and 6.5 cm. respectively. Roentgen-ray showed a considerable area of disease involving the right ilium, ischium and femur down to the middle third of the shaft. He died on February 14, 1937.

Case 13. C. C., female white child, aged 11 years, was admitted to Neponsit Beach Hospital on May 9, 1935. About six years before, child had had Pott's disease and had been placed on a Bradford frame for six months and then in a cast for over a year. At the end of this time the tuberculous disease of the spine was apparently quiescent and had continued inactive to the date of admission. Three years before she experienced pain in the left hip. She was immobilized in a plaster spica cast until the fall of 1934 when it was removed and she was allowed to be up and about. Several months later the activity in the left hip recurred. Suppuration and discharging sinuses developed.

On admission the child was very pale and thin, weighing 53 pounds. She showed classical signs of amyloidosis. The liver and spleen were 1 cm. The left thigh was in flexion and adduction and presented about it numerous discharging sinuses. Shortly after admission the child's condition became progressively worse. On September 19, 1935, the liver was 8 cm., the spleen 5 cm. Roentgen-ray showed marked adduction and vacuolization in the shaft, neck, head and great trochanter of the left femur. There was apparently no pelvic wall left to the hip joint. Liver therapy was then instituted. Her amyloid condition improved slowly with short periods of remission. On March 13, 1936 the general condition was fair. The liver and spleen were 5 cm. and 2 cm. respectively. Roentgen-ray showed greater destruction of the acetabulum, head, neck and great trochanter of the left femur than was present in the previous plates. A rather large vacuole was present at the junction of the great trochanter and the shaft. The temperature continued to be moderately elevated and her sinuses discharged profusely. She soon began to object to the liver therapy and vomited frequently. As a result she took very little liver. By October 15, 1936, it was noted that the liver was 6 cm. and the spleen 4.5 cm. She left the hospital against advice shortly thereafter (November 8, 1936).

COMMENT

Thirteen children with moderately advanced to advanced amyloidosis have been treated with a desiccated powdered whole liver product administered in a suitable vehicle in doses of 4 to 8 grams, three times a day. The children as a rule tolerated the liver preparation fairly well. There

TABLE I
Summary of Results with Liver Therapy in Secondary Amyloidosis

Case	Age at Onset of Primary Disease (Years)	Nature of Primary Disease	Duration of 1° Disease to Time of Appearance of Amyloidosis (Years)	Duration of 1° Disease After Onset of Amyloidosis (Years)	Age at Onset of Amyloidosis (Years)	Duration of Amyloidosis Before Treatment (Years)	Duration of Amyloidosis During Treatment (Years)	Results of Liver Therapy in Individual Cases	Remarks
1	7	Tbc. spine	4	5	11	3	2	Cured	Subsidence of amyloid: slow improvement in 1° disease
2	7½	Tbc. knee	2	4	9	1½	2½	Cured	Ditto
3	3½	Tbc. spine	2½	3½	6	1	1½	Died	Liver therapy taken irregularly and poorly
4	6(?)	Tbc. spine	1(?)	3	7	2	2	Died	
5	7½	Tbc. hip	1½	4½	9	2	3½	Died	Left hospital and received no therapy for 8 months
6	7	Tbc. hip	2½	4	9½	2	1½	Cured	1° infection active for nine months after cure of amyloidosis
7	2½	Tbc. knee	1	6½	3½	1½	2	Cured	1° infection was present for 3 years after cure of amyloidosis
8	7½	Multiple chronic osteomyelitis	2½	5½	10	3	3	Cured	1° infection was present for one year after cure of amyloidosis
9	3	Tbc. hip	2½	7*	5½	3	6½*	Much improved	1° infection still present and active
10	4	Tbc. hip	4½	4½*	8½	1	3½-4	Cured	1° disease still present and active
11	7	Tbc. hip	3½	6½*	10½	1	5½*	Much improved	1° infection still active, liver and spleen just palpable
12	9	Tbc. hip	1	2½	10	1	2½	Died	Took liver therapy poorly and irregularly
13	8	Tbc. hip	3	2*	11	1	1½	Condition unchanged	Discharged against advice

* Disease still present. Duration specified is that up to May 1937.

were a few, however, who were unable to take this medicament continuously. Frequently nausea and vomiting set in and forced the discontinuance of its use for periods varying between 14 days to two or three months. It was these children, too, who did not show the striking benefits that were evident in the others. A summary of the results is recorded in table 1.

Complete recovery from generalized secondary amyloidosis was obtained in six of the juvenile patients. With the exception of two phenomena, i.e. albuminuria and the Congo Red test, all other signs and symptoms indicative of the existence of amyloidosis disappeared completely within an average period of two to three years after institution of liver therapy. These children are today alive and well with no recurrence of symptoms after a lapse of two to five years or more. In two other children there has occurred to date significant clinical improvement and all indications point to complete recovery in the near future.

In one subject who received the liver therapy for only 13 months, the lardaceous condition has remained essentially unchanged. The situation was somewhat complicated by the fact that she was taking the preparation very irregularly due to its unpleasant taste and the development of nausea and vomiting.

The remaining four children died. Two of them (cases 3 and 4) were in a very advanced state of amyloidosis and received the product irregularly only over a period of 16 and 7 months respectively. Even in these cases there was improvement in the amyloid state as evidenced by the disappearance of edema and ascites and by the diminution in the size of the liver and spleen. However, the severity of the primary condition was responsible for the fatal termination. In the third child (case 5) there occurred significant improvement. After 15 months of liver therapy, the liver and spleen were no longer palpable. With the advent of erysipelas, the tuberculous infection and the amyloidosis were both aggravated. The severity of the primary disease retarded the amelioration of the amyloidosis by liver therapy. The child's condition was unimproved at the time of his discharge from Neponsit Beach Hospital. His parents insisted upon taking him home. He died within eight months after his return home. No liver therapy was given during his stay at home.

The fourth child (case 12) had a malignant tuberculous infection. This, coupled with his inability to take the liver therapy, was probably responsible for our failure. The unavailability of a potent liver extract for parenteral administration was the reason for not using such a preparation in the cases that objected to taking the medicament orally.

The primary disease in all these children was very severe. Symptoms indicating activity of the infection, e.g. fever, continued increasing destruction of bone, discharging sinuses, local pain, tenderness, limitation of motion and pain upon movement, were present during the period of treatment and continued for a considerable time even after striking recession of the symptoms of amyloidosis. In four patients who recovered from their amy-

loidosis, elevation of temperature, considerable discharge from sinuses and local signs of active infection persisted for periods of from eight months to three years after clinical cure of the amyloid state was obtained. In the other children, definite retrogression of the amyloid symptoms occurred even during the height of the initial infection. These observations speak against the suggestion that improvement of the amyloid state is attributable to improvement of the concurrent tuberculous condition. The improvement of the amyloidosis and the evidences of its apparent resorption preceded by months or even years the improvement in the primary infection, although the latter did, in time, occur. Such improvement of the primary infection is to be expected in view of the fact that the existence of amyloidosis aggravates the initial disease and that the degree of severity of the latter would decrease with melioration and removal of the lardaceous material. To disregard these clinical manifestations and to attribute the favorable clinical course of the treated amyloidotic children to the subsidence of the primary disease and not to the liver therapy we therefore believe is unwarranted. Rosenblatt¹³ citing a case of recovery, which was treated with a liver product and in which the primary disease showed almost simultaneous improvement, ascribes the results solely to the subsidence of the underlying condition. This interpretation is based on his conception that amyloidosis simply reflects a very advanced state of the initial disease, but that the lardaceous condition per se does not exercise to a significant degree any serious effect upon the organism. This stand is untenable in view of the marked renal, gastrointestinal, hepatic, hematological and chemical functional disorders and the organic changes which are present in generalized primary and secondary amyloidosis. Further, in our series of 68 cases of amyloidosis, receiving no liver medicament, all died within two to three years.¹⁴ Autopsy in most instances of this group indicated that the amyloidosis rather than the underlying tuberculous infection was directly responsible for the fatal outcome. In fact, the tuberculous process in such patients was distinctly less extensive and severe than it was in a comparable series of non-amyloidotic subjects in whom death was the direct result of the acid-fast infection. Similar observations, that the degree of amyloidosis and its fatal effects are not dependent on the extent or severity of the incitant tuberculosis, have recently been made independently by Lipstein and Auerbach.¹⁷

In the treated group, in addition to the six cases of recovery after the onset of the amyloid condition, the rest showed considerable prolongation of their survival period. This in itself indicates a marked retarding effect of the liver preparation upon the lardaceous process and is in harmony with the observation that white mice show definite retardation and resorption of the amyloid with the use of the liver product.^{15, 16}

Very soon after the institution of the liver therapy, striking improvement of the amyloidosis was observed in all cases. At the beginning of the therapy, for short periods varying from three to six months, the im-

provement was more marked. It then continued at a much slower rate either with steady progress or with periods of remission. In some instances, the relapses were of the same magnitude as the illnesses preceding treatment. Persistence of the liver medicament, however, led to amelioration or recovery from amyloidosis in most instances. This point is worth stressing. One should not be discouraged at failure to obtain uninterrupted improvement. One should not suspend treatment when one encounters severe recrudescence of amyloidosis even though it may be of long duration. Persistence in therapy over a period of several years may eventually result in recovery. When one realizes the vagaries of the primary disease constantly operating to effect amyloid formation, one cannot always expect uninterrupted improvement.

The first evidences of improvement of the amyloidosis are a reduction in the size of the abdomen and of the liver and spleen, and the diminution of the dilatation and tortuosity of the superficial epigastric veins. Subsequently there occurs improvement in the general condition and appearance of the patient including the color of the skin and mucous membranes. After the initial subsidence of the various manifestations of amyloidosis, there will be a relatively longer period of one or more years when the signs may remain practically unchanged or may recede very slowly. In the event of a severe and prolonged relapse of the primary disease, many of the symptoms may return and even become aggravated. With continuance of liver therapy, total recession will probably take place.

A possible explanation for the early more rapid retrogression of the lardaceous condition may be that the more recently formed amyloid is less stable and resistant to physico-chemical influences and is more rapidly resorbed. It is possible that it is this relatively newly deposited substance which is at first removed. On the other hand the longer the amyloid resides in the tissue, the more stable does it become^{16, 18}; and the more difficult does it become to disintegrate and eliminate this material. This may account for the apparent retardation during the second stage in the resorption of amyloid.

The marked albuminuria which has been present in all the treated children persisted in most cases long after the complete disappearance of the other signs and symptoms of amyloidosis. Usually not until two to five years had elapsed after apparently complete clinical recovery, did the urine become free from albumin. The quantitative decrease proceeded at a very slow rate. The persistence of the albuminuria after clinical recovery from amyloidosis, is, in most instances, probably due to the continuance of the primary disease. One of our children (case 6) still has marked albuminuria with numerous leukocytes and an occasional erythrocyte in his urine four years after the total disappearance of all other signs of amyloidosis. He is apparently in good health and complete examination including an extensive genito-urinary investigation fails to reveal any other

condition to account for this phenomenon except possibly structurally altered kidneys, the after effects of renal amyloidosis.

The Congo Red test was positive (100 per cent withdrawal) in all the treated children before institution of liver therapy and in recovered cases, even at the time when there were none of the other symptoms or signs of amyloidosis. In two subjects in whom repeated Congo Red tests were performed, there was a gradual decrease in the percentage withdrawal of the dye from the blood stream. In both patients the sharp reduction in the dye absorption occurred only after the disappearance of the primary disease. However, within 16 months after the latter phenomenon, the test was completely negative (i.e. 100 per cent retention of Congo Red in the blood stream). In passing, it may here be said that the presence of Congo Red absorption of even 70 per cent of the injected dye has been reported in cases without amyloidosis as proved by detailed autopsy examination.¹⁷ Three such cases showed 90 to 100 per cent withdrawal of the dye. The Congo Red test must therefore be considered of less significance in the diagnosis of amyloidosis, in the absence of signs and symptoms of the disease, than is generally accepted.

The very marked anemia which usually is present in these children became less severe but never quite disappeared until recovery was complete. The blood-chemical findings of decreased total serum protein and inversion of the albumin-globulin ratio, obtained in all cases of amyloidosis, returned to normal values very slowly after other clinical symptoms had disappeared. In one case (case 7) a return to normal was observed only four years after clinical cure. The primary infection is in the main responsible for the persistence of the anemia and the serum protein changes.¹⁰

DISCUSSION

The earliest stages of amyloidosis cannot be determined clinically with certainty. It is often a matter of guesswork. It is probable that the initial changes are those which are common to all infections and that gradually with continuance of the underlying cause, changes develop further until they reach the transformation which is known pathologically as amyloid. Even at this point the process does not stop. This process, except possibly in the very advanced stages, may be reversible. With the disappearance of the causal factor and provided no permanent secondary changes have occurred, amyloid may be resorbed and complete recovery may follow. This is substantiated by animal experimentation¹⁰ and by clinical reports of cures.¹⁻¹³ There has been one drawback to the above concept. Once unquestioned advanced amyloidosis had set in, the condition invariably seemed to progress to a fatal termination. This is indicated by the very few reported cases of recovery in the literature. This outcome is the result of two reciprocally acting factors. Amyloidosis occurs in severe and prolonged infections which run an unabated course and in themselves cause death; and secondly

the occurrence of the lardaceous condition not only aggravates the primary disease but causes great functional disturbances in the individual, reducing his vitality and general resistance. It is for these reasons that a steady unfavorable march of events is noted in almost all cases of amyloidosis.

In order to prevent any possible criticism of our results with the 13 treated children, only those subjects were selected who had pronounced symptoms of amyloidosis, which definitely progressed during the control period of six or more months, and whose primary disease was active and was not responding to any of the other measures. It was with the intention of making certain that no other factor, except the liver therapy, could possibly be considered as instrumental in influencing the course of the disease. Previously all our cases of amyloidosis although under identical management except for the liver administration, died. The six cases of complete cure, and the two children with substantial improvement, indicate definite benefit that is to be derived from liver medicament. Furthermore, definite prolongation of survival period in those others who died with some amelioration of their amyloid condition, indicated a favorable influence of the remedy. That resorption of amyloid occurs even during the active phase of the primary disease as indicated by elevation of temperature, discharging sinuses, local symptoms and roentgen-ray findings of progressive destruction, must lead one to attribute a beneficial effect of liver therapy upon generalized secondary amyloidosis.

Parenthetically it may be added that more cases of recovery with more rapid resorption of amyloid would probably have occurred if the subjects chosen for treatment had not been so severely affected or had not been allowed to progress untreated for so long a period. Furthermore, although such studies are difficult to evaluate, prevention of amyloid formation may be possible by administering liver therapy to patients with severe suppurative primary infection. The results in three such selected children tended to indicate such an effect. All these probabilities are indicated both by the results obtained in this study and by previous animal experiments with early amyloid.¹⁶

Organotherapy consisting chiefly of liver, spleen or bone-marrow feeding has been used by many workers in the treatment of tuberculosis and other chronic infections. Ruttgers and Kamsler,²⁰ Loeffler,²¹ Ropschitz,²² Kuss,²³ Fliegel,²⁴ Armand-Dellile²⁵ fed raw spleen and obtained good results in the treatment of children with extensive tuberculosis of the bones and joints. Similar beneficial effects and rapid improvement with the use of splenic extracts were noted by Bayle²⁶ and Dunham.²⁷ Dejust-Defives²⁸ found that the administration of combined extracts of liver, spleen and kidneys to tuberculous patients resulted in remarkable improvement of the blood and the general condition. Experimental confirmation of the usefulness of splenic extract in guinea pigs infected with tubercle bacilli was obtained by Bayle²⁶ and Watson.²⁹ Newton³⁰ observed favorable influence

upon the general condition, appetite and blood of tuberculous patients receiving liver extract. Faust and his co-workers³¹ have shown that the feeding of raw liver or a powdered liver extract to dogs infected with *Endameba histolytica* exercised a decidedly ameliorative effect. Becker and Morehouse³² by administering dried powdered liver retarded the development of coccidian infections in rats and chickens fed with oöcysts.

Many workers have stressed the rôle of the reticulo-endothelial system in infections. The condition of this important specialized tissue which is scattered throughout the body but is predominant in such organs as the liver and spleen, is a very important determining factor in the treatment of infectious disease, particularly of tuberculosis. Any measure that would increase its functional action or supplement it qualitatively should enhance the organism's ability to cope with the infection. With this view in mind Wedekind³³ advocated the intravenous administration of a suspension of fine particles of carbon in sub-toxic doses in the treatment of pulmonary tuberculosis; and Schurer-Waldheim³⁴ proposed irradiation of the spleen. Schliephake and Sincke³⁵ noted that the administration of splenic extract to rats and guinea pigs increased the storage capacity of the reticulo-endothelial system for trypan blue. These agents as well as others stimulated the reticulo-endothelial system or caused the production of hypertrophy and hyperplasia of the elements of this system, a stage morphologically which precedes the appearance of experimentally produced amyloid (so-called precursory stage).¹⁶

Amyloidosis can be produced in certain animals by the parenteral injection of a variety of substances.³⁶ These animal studies shed much light on the nature of this pathological condition. Several theories are advanced by respective workers.³⁷⁻⁴¹ Without engaging in any discussion of the relative merits of each, the authors wish to offer one that appears most plausible to them, based on the work of others as well as their own. A more detailed discussion of it appears in other publications.^{14, 16}

Amyloidosis is the result of a relatively long-continued disturbance of endogenous protein metabolism. In any condition where there occurs persistently an excessive destruction of tissue protein, such as during chronic infections or wasting diseases, amyloidosis may set in. Exogenous protein metabolism is performed by the alimentary tract and its accessory organs such as the liver, etc. The tissue cells also participate in this process. However, it is the gastrointestinal tract with its wealth of chemical substances that, in the main, disintegrates the large protein bodies into smaller and assimilable compounds. With few exceptions, the gastrointestinal system can adapt itself and can, relatively easily, digest indefinitely varying amounts of protein material. In the matter of endogenous protein metabolism, the human being and most animals have not such relatively unlimited powers. The metabolic products consist of different protein fractions, many of which are not of a chemical form which can be assimilated or utilized or eliminated without further bio-chemical action. While the tissue

cells do possess enzymes and other lytic agents, they are limited in this respect both qualitatively and quantitatively. However, this shortcoming is to a great extent overcome by the reticulo-endothelial system. The latter, with its wealth of specialized cells, has the capacity of taking up (phagocytizing) these non-utilizable products and altering them into chemical forms which can be metabolized by the tissue cells or of retaining these so-called foreign substances, thereby permitting their original elimination without unduly disturbing the organism. This remarkable reticulo-endothelial system can undergo hypertrophy and hyperplasia in response to such increased demands. Although its reserve power is great, this hypertrophy and hyperplasia cannot go on indefinitely. A point is eventually reached when it decompensates though this may vary greatly with the individual.

In any condition where excessive destruction of tissue protein occurs, such as in chronic tuberculosis, the organism is called upon to take care of the various kinds of split protein molecules. The reticulo-endothelial cells, playing an active rôle in this endogenous metabolic process, are at first able to dispose of these substances with relative ease. As this demand continues or increases over a very long period of time, the phagocytic cells begin to lag or are unable to take care of the material as fast as it is being formed. At this stage increasingly larger masses of the material reside in each cell until these fuse with one another forming giant cells which finally disintegrate and, together with the amyloid substance, form extra-cellular deposits. The exhaustion or the inability (decompensation) of the fixed and wandering cells of the reticulo-endothelium to cope with the demands causes further extra-cellular deposition. Hypertrophy and hyperplasia cannot continue indefinitely. Phagocytosis cannot keep pace with the continued supply of newly liberated protein. Eventually the excessive accumulation of this material interferes with the function of the organ where it resides, produces a slow but progressive atrophy, and finally a necrosis of the normal tissue with resultant somatic death.

The action of the liver substance in its favorable effect upon resorption of amyloid may be one of supplementing the important component or components which are necessary for the continuance of this reversible process; or it may stimulate further the reticulo-endothelial system; or in some other unknown manner it may affect endogenous protein metabolism. It is significant that in animal experiments liver extract produced marked reticulum cell hyperplasia.

To ascribe amyloidosis merely to a hyperproteinemia is to disregard consideration of the dynamics of its formation and to overlook the possibilities of therapy which attention to the reticulum cell changes suggested experimentally to others⁴² and to ourselves; and which the present report of the cases treated and cured by the use of the reticulum cell enhancing agents strongly confirms.

Aside from all theoretical considerations, the present study indicates that amyloidosis complicating chronic suppurative disease is, in human

beings, a clinically reversible process in all but the extremely advanced phases. True, one must stubbornly persist in using liver therapy; but with such or similar therapy, it is no longer necessary to view cases of recovery from amyloid as isolated and unusual as has been the opinion hitherto. And it is no longer necessary to regard this disease as incurably progressive. The experimental evidence previously reported and the treated cases reported here indicate that amyloid may be a curable malady.

SUMMARY

1. Thirteen cases of amyloidosis secondary to chronic suppurative disease in children were treated with oral administration of powdered whole liver extract. Of these, six cases have now been completely free of all clinical signs of amyloid for periods of from eight months to six years. Two patients have shown enormous improvement. Four children in advanced stages of amyloid and tuberculous disease when first seen have died. These four took the liver preparation very poorly and irregularly. Two of the dead subjects were in an extremely advanced state and died very shortly after the institution of therapy. One child, whose amyloidotic condition was essentially unchanged, left the institution before a sufficient period of therapy had elapsed.

2. The clinical improvement of the amyloid state occurred during the presence of the active suppurative infection; and the clinical cure preceded, by a very substantial interval as a rule, the subsidence and disappearance of the primary disease.

3. Emphasis is laid upon the fact that liver therapy must be persistently employed, despite absence of clinical improvement, for periods of three or more years before failure is admitted. It is pointed out that clinical amelioration of the amyloidosis is not regularly progressive and it is suggested that this may be a function of the variable chemical composition of amyloid of different ages, as well as of the relapsing nature and severity of the primary incitant infection.

4. Diminution in the size of the liver and spleen are usually the first signs of improvement under therapy. The other symptoms recede slowly.

5. The rôle of the reticulo-endothelial system and disturbance of endogenous protein metabolism in the formation and resorption of amyloid are discussed and a theory is advanced as to the mechanism involved. The rôle of the liver product in the resorptive process, as a factor in this mechanism, is indicated.

6. It is pointed out that amyloidosis is a reversible process. Experimental evidence and the here reported cases of recovery indicate that amyloidosis is a curable malady.

Note. In the year that has elapsed since this paper was submitted for publication, cases 9 and 11 (table 1) have been completely cured of all signs of amyloid disease and are entirely symptom-free as far as this disease is concerned. The tuberculous sinuses, however, are still draining profusely, their temperature continues elevated,

and the roentgenograms show increasing bone destruction. The other living cases have remained entirely free from signs or symptoms of amyloid disease without further liver therapy except in case 10 where, because of continuing activity of considerable degree of the tuberculous process, liver therapy is still being used. To the combined figures in the columns (table 1) labelled "Duration of Amyloidosis Before Treatment" and "Duration of Amyloidosis During Treatment," i.e., length of survival after the diagnosis was established, one year should be added in the cases 1, 2, 6, 7, 8, 9, 10, and 11.

BIBLIOGRAPHY

1. KRETZSCHMAR, P. H., and WESTBROOK, B. F.: A case of chronic empyema with extensive amyloid degeneration—recovery, *Proc. Med. Soc. County Kings*, 1880, v, 343.
2. OWEN, I.: Recovery from advanced lardaceous disease, *Proc. Med. Soc. London*, 1886, ix, 18.
3. GAIRDNER, W. P.: In discussion of F. Delafield's paper "On the diseases of the kidneys, popularly called Bright's disease," *Trans. Assoc. Am. Phys.*, 1891, vi, 149.
4. HARRINGHAM, W. P.: *Kidney diseases*, 1912, Oxford University Press, Oxford, page 353.
5. NATHAN, M.: Ueber die klinische Diagnose mittels Kongorotinjektionen, *Munchen. med. Wchnschr.*, 1928, lxxv, 1883.
6. WALDENSTROM, H.: On the formation and disappearance of amyloid in man, *Acta chir. Scandinav.*, 1928, lxiii, 479.
7. WALKER, G. F.: A case of recovery from amyloid disease, *Lancet*, 1928, ii, 120.
8. GRAYZEL, H. G., JACOBI, M., MASLOW, H., and WARSHALL, H. B.: Experimental studies in amyloidosis, *Proc. Soc. Exper. Biol. and Med.*, 1930, xxviii, 172.
9. WHITBECK, B. H.: Liver meal in the treatment of amyloidosis in surgical tuberculosis, *Jr. Bone and Joint Surg.*, 1932, xiv, 85.
10. HABEIN, H. C.: Amyloidosis: report of a case in which the patient recovered, *Proc. Staff. Meet., Mayo Clinic*, 1934, ix, 261.
11. REIMANN, H. A.: Case of amyloidosis with recovery, *Jr. Am. Med. Assoc.*, 1935, civ, 1070.
12. KENNEDY, W. R.: Renal amyloidosis, *Canad. Med. Assoc. Jr.*, 1935, xxxiii, 385.
13. ROSENBLATT, M. D.: Recovery from generalized amyloidosis secondary to pulmonary tuberculosis—report of a case, *Arch. Int. Med.*, 1936, lvii, 562.
14. GRAYZEL, H. G., and JACOBI, M.: Generalized amyloidosis secondary to tuberculosis. (To be published.)
15. GRAYZEL, H. G., JACOBI, M., WARSHALL, H. B., BOGIN, M., and KRAMER, B.: Clinical and experimental studies in amyloidosis, *Acta Paediat.*, 1933, xxvi, 177.
16. GRAYZEL, H. G., JACOBI, M., WARSHALL, H. B., BOGIN, M., and BOLKER, H.: Amyloidosis: experimental studies, *Arch. Path.*, 1934, xvii, 50.
17. LIPSTEIN, S., and AUERBACH, O.: Congo Red test, *Quart. Bull. Sea View Hosp.*, 1937, ii, 120.
18. WELLS, H. G.: *Chemical pathology*, ed. 5, 1925, W. B. Saunders Company, Philadelphia.
19. GRAYZEL, H. G., JACOBI, M., and MILLER, P.: (To be published.)
20. RUTTGERS, P., and KAMSLER, A.: Über Milzdiät bei Tuberkulösen, *Beitr. z. Klin. d. Tuberk.*, 1929, lxxii, 68.
21. LOEFFLER, F.: Milzverfütterung bei citrigen Knochen- und Gelenkerkrankungen, *Zentralbl. f. Chir.*, 1929, lvi, 2946.
22. ROPSHITZ, A.: Über eine bequeme Durchführungstechnik der Rohmilztherapie bei destruktiver Gelenkstuberkulose, *Med. Klin.*, 1930, xxvi, 166.
23. KUSS, H.: Milztherapie bei Knochen- und Gelenktuberkulose, *Med. Welt*, 1929, iii, 1334.
24. FLIEGEL, O.: Calf spleen diet in treatment of suppurative tuberculosis of joints, *Jr. Bone and Joint Surg.*, 1930, xii, 788.
25. ARMAND-DELLILE, P. F.: Action favorable d'extraits spléniques sur certaines formes évolutives de la tuberculose pulmonaire chez l'enfant, *Rev. d. l. Tuberc.*, 1928, ix, 256.

26. BAYLE, J. C.: L'Opothérapie splénique. Traitement de choix de la tuberculose, *Presse Med.*, 1925, lxxvi, 1266.
27. DUNHAM, R. W.: The effect of splenic extract and bone marrow on the blood picture in pulmonary tuberculosis, *Am. Jr. Med. Sci.*, 1925, clxx, 394.
28. DEJUST-DEFIVES, S.: Etude clinique de l'action simultanée des extraits foie, rein, rate sue diverses anémies (Anémies post-hémorragiques. Anémies de la tuberculose), *Progres Med.*, 1930, lviii, 189.
29. WATSON, G. F.: Raw spleen extract in tuberculosis, *Am. Rev. Tuberc.*, 1935, xxxii, 312.
30. NEWTON, H. F.: Über die Beeinflussung sekundärer Anämien bei Tuberkulösen durch Leberextrakte, *Klin. Wchnschr.*, 1928, vii, 1062.
31. FAUST, E. C., and SWARTZWELDER, J. C.: Use of liver extract intramuscularly in the course of acute amebiasis in dogs, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiii, 514.
32. BECKER, E. R., and MOREHOUSE, N. F.: Liver as a source of vitamin G, *Science*, 1936, lxxxiii, 530.
33. WEDEKIND, T.: Die Bedeutung des Reticuloendothels für die Tuberkulose-therapie, *Klin. Wchnschr.*, 1930, ix, 822.
34. SCHURER-WALDHEIM, F.: Milzbestrahlung und retikulo-endothelialer Apparat, *Wien. klin. Wchnschr.*, 1930, xliii, 201.
35. SCHLIEPHAKE, E., and SINCKE, G.: Über die Wirkung von Milzextrakten auf das reticulo-endotheliale System, Gezeigt an der Trypanblauspeicherung, *Klin. Wchnschr.*, 1931, x, 346.
36. HEROSE, K.: Experiments in the artificial production of amyloid, *Bull. Johns Hopkins Hosp.*, 1918, xxix, 40.
37. KUCZYNSKI, M. H.: Neue Beiträge zur Lehre vom Amyloid, *Klin. Wchnschr.*, 1923, i, 727.
38. SMETANA, H.: The relation of the reticulo-endothelial system to the formation of amyloid, *Jr. Exper. Med.*, 1927, xlv, 619.
39. JAFFEE, R. H.: Amyloidosis produced by injections of proteins, *Arch. Path. and Lab. Med.*, 1926, i, 26.
40. LETTERER, E.: Experimentelle Studien über Art und Entstehung des Amyloids, *Zentralbl. f. inn. Med.*, 1926, xlvii, 417.
41. EKLUND, C. M., and REIMANN, H. A.: The etiology of amyloid disease, *Arch. Path.*, 1936, xxi, 1.
42. CAVALLACCI, G.: Osservazioni sull' amiloidosi sperimentale, *Pathologica*, 1934, xxvi, 303.

THE RELATIONSHIP OF AGE TO THE CONCENTRATION OF ACID SOLUBLE PHOSPHORUS IN HUMAN TISSUES *

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IN a preliminary report, Struck and Visscher¹ noted an inverse relation between the ages of two groups of rats and the mean concentration of total acid soluble phosphorus in muscle. Since these two groups were not of homogeneous origin, the work was repeated and extended. A part of the results were embodied in a preliminary report by Bartoli, Cohen and Struck,² confirming the earlier findings.

A survey of the literature on the general subject of chemical changes with aging shows a badly confused state of knowledge.

The fact that the concentration of acid soluble phosphorus of human serum decreases under normal conditions from an average of approximately 5 mg. per cent in infancy to 3.5–3.7 mg. per cent in the adult has long been known. Similar changes have recently been demonstrated in horses by Pearson³ and in chicks by Elvehjem and Kline.⁴ In cattle the concentration of inorganic phosphorus increases slightly from the second to fourth month of life, remaining fairly constant until the tenth month, after which time there is a gradual decline.⁵

Other constituents of blood have also been studied in recent years, and in some cases similar changes have been found to occur. Thus, Currado⁶ has found that the uric acid concentration of the blood of individuals over 70 years of age is definitely lower than that of healthy, young adults. Unfortunately, his data do not include values for infants or children. A change in the copper content of the blood during the first few months of life in humans has been found by Lesne, Zizine, and Briskas.⁷ Apparently there is a fall during intrauterine life, followed by a distinct rise during the first two months of postnatal life. The cholesterol content of human serum has been studied by Eck and Desbordes,⁸ who found that it tends to increase with age, while the cholesterol dissolving power of the blood also increases; the tendency was reversed in individuals over 60 years of age. Kalabukhov and Rodionov⁹ have found that there is a decrease in water content of the blood, together with a decrease in blood acidity and the size of the erythrocytes. The number of cells and the glucose concentration, however, show increases. Kurado¹⁰ has also found this change in water content of the blood of mice.

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Watchorn¹¹ has found that the serum calcium of adult rats is very slightly lower than in young animals, and, while the magnesium content of serum of males also decreases slightly, that of the females remains constant. In the human, however, Kirk, Lewis and Thompson¹² have been unable to find any change in calcium. Glutathione¹³ and plasma lipids¹⁴ have been found to remain constant with respect to age in men. Similarly, no significant changes in urea, non-protein nitrogen, creatinine, uric acid, glucose, sodium, chloride, or ash of chicken blood could be found by Heller and Pursell¹⁵ throughout the life cycle. Certain other constituents were, however, found to change, particularly during the time of egg laying.¹⁶

The chemical composition of tissues other than blood has received some attention, but in very few studies has there been any complete investigation of the composition of the tissues over the entire life span of the species studied. This fact is easily explained by the great difficulties involved in maintaining a large enough colony for a time sufficient to give statistically significant results. Thus most of the results presented in the papers reviewed below are based on data from autopsy specimens, or in nonhomogenous colonies of animals. The possible errors involved in this method are, of course, obvious.

Roche and Leandri¹⁷ report that in the long bones of the rat the phosphatase content is greatest during the period of most active growth, and that, as growth slows and finally ceases, the phosphatase decreases gradually to a constant value. However, no data are presented for extremely old animals. Burns and Henderson¹⁸ have studied the mineral composition of the bones of young pups and kittens, and have found, as was to be expected, that the calcium content rises until growth of the bone is complete. The interesting fact to be noted in their report is that immediately after birth in both pups and kittens there is a short period when the mineral content of the bone decreases. Whether this is a general finding, or may have been due to the particular condition of the experiment, or some other factor, cannot be stated. This point will bear further study.

Blume¹⁹ reports finding that the glycogen content of human hearts is markedly higher in infants than in adults.

Several investigators have studied the variations in enzyme activity of various tissues with the age of the animal. Pearce²⁰ has studied the oxygen consumption of excised liver, kidney, and cardiac tissue from a genetically pure strain of mice at two age periods: 4 to 9 weeks, and at 50 to 60 weeks. He finds significant decreases in all three tissues in the older animals, the greatest decrease occurring in the liver, the least in the kidney. A similar type of study has been made on *Drosophila* by Sekla,²¹ who finds that the esterolytic processes increase from birth to a mean age slightly over maturity, and then decline. Again, Falk and his colleagues²² have found extracts of whole rat show increasing lipase activity from birth to maturity, after which there is a steady drop to the oldest animals studied, three years. This general trend is further confirmed by Lebensohn,²³ who reports that in vitro tis-

sue cultures of old animals show much slower growth rate and carbohydrate utilization than tissues from young animals. The rates are also dependent in the same way, although to a lesser degree, on the age of the animals from which the plasma was obtained for the culture.

The energy metabolism of humans is known to vary with age, there being a definite rise in metabolic rate during prepubertal life, followed by a decline, at first fairly sharp, later more gentle, but continuing throughout life. This same type of variation has been shown by Davis²⁴ to hold for the white rat.

A change in the proportion of liquid and solid fatty acids of subcutaneous tissue has been found by Stolfi.²⁵ The subcutaneous tissue becomes richer in oleic acid relative to solid fatty acids as age increases, the change taking place chiefly during early life.

Tung-Pi Chow and Adolph²⁶ have reported analyses on tissues from five cadavers aged three months to "adult," and all tissues examined, except the pancreas, show marked decreases in copper content. Interestingly, Zondek and Karp²⁷ have found that the iron content of cells increases with age in such tissues as liver, kidney, and testis. This increase takes place over a relatively short period of time in the life span and always during the middle or late adult life of the animal. During the remainder of the life span the iron content is constant.

Greenberg and Tufts²⁸ have analyzed the entire carcass of the rat for magnesium and water at various ages, and have found that there is a rapid increase in magnesium from birth to about four weeks of age. The magnesium content remains relatively constant during the next seven to ten weeks, after which time there is a steady decline through the thirtieth month of life. The water content decreases progressively during the 30 month period studied. While these data are of great interest, they do not cover the entire life span of the rat, and, more important, they give no clue as to where the changes take place. A similar type of study has been made by McCay and his colleagues²⁹ in the brook trout. These investigators found that the calcium and phosphorus content of the entire body of the trout show marked increases from one day old (eggs) to 10 months old. Winter³⁰ has found that during the first 31 days of life the total chloride content of the body of the rat decreases about one-third. No data are presented for older animals, however.

Cole and Koch³¹ have studied the phosphorus fractions of striated muscles of rats, and have found that there is a rapid increase in creatine phosphate content from birth to two or three weeks after weaning, a change which may be due to the relatively great increase in exercise during this period. They did not find any significant change after the value had reached its maximum through 168 days of life.

The central nervous system of the rat has been the subject of several studies of this nature. Koch and Koch³² have found that certain definite changes in chemical composition of the brain of the rat occur during the first 210 days of life. The total solids increase about 100 per cent, and in the

solid matter the proteins decrease, while the phosphatids, cerebroside, and sulfatids all show increases. The total sulfur and total phosphorus decrease as well. In the case of the phosphorus, the decrease is due to the protein and water soluble phosphorus, since the lipoid phosphorus shows a marked increase over this period. Hatai³³ has analyzed the brains of rats over a 380 day period, and has found that, calculated as per cent of moist tissue, the non-protein nitrogen of the brain remains relatively constant, while showing a definite decrease when calculated as per cent of dry tissue. A more recent study by Epel'baum³⁴ shows that during the first seven days of life the total phosphorus and acid soluble phosphorus of the brain of the rabbit increase markedly, but by 30 days the values have decreased to the adult level.

Max Bürger³⁵ has made numerous analyses of various tissues of different species and has found that frequently the curve obtained by plotting the log of the age of the animal against the log of the per cent of the constituent is a straight line. Thus, the per cent of dry residue in human skin and rib cartilage, in cattle lens and cornea, all show increases, although the gradients of the curves are different. The per cent of nitrogen in human skin and rib cartilage, and in cattle lens and skin, likewise are increased. Similar results were found for calcium content of various tissues. Human erythrocytes show definite increase in fragility with age, according to the same author. Studies by Keuenhof³⁶ have shown that the opening of the aorta of the horse shows a marked increase with age, and that the calcium and cholesterol content show approximately 100 per cent increases from 1 to 25 years of age. The cholesterol content of the human aorta shows a marked increase from 1 to 80 years of age.

Moulton³⁷ has studied the water, nitrogen and ash contents of the fat free animals of several species with respect to age of the animal. All curves have the same general form. In general, the water content decreases rapidly to a fairly constant level reached very early in extra-uterine life, the ash and nitrogen content increasing to a constant level reached at the same time as the water content. The author concludes that the animals should be compared on the fat free basis, and on this basis it can be shown that "mammals show a rapid decrease in relative water content, an increase in protein (nitrogen) and ash content from earliest life until the time of chemical maturity is reached. At this time the change becomes rather suddenly less and nearly constant composition is shown. Mammals vary in composition at birth. Those relatively mature have a low water content, and those less mature a high water content." Mammals reach chemical maturity at different ages, but these ages are a fairly constant relative part of the total life cycle, about 4.5 per cent of the cycle being the average.

Bernstein³⁸ has endeavored to express the changes during growth mathematically. He found that certain changes—the increase in cholesterol and insoluble globulin, and the decrease in water—can be correlated to a degree

with the physiological age of the individual, and that those individuals in whom these changes were, for any cause, accelerated tended to die young.

Chanutin³⁹ finds that during the period of active growth of the rat the creatine concentration is markedly increased. Fat and ash concentrations reach a maximum at about the twentieth day of life, after which there is a gradual decrease. The nitrogen concentration he finds to be constant throughout life. His analyses, however, do not sufficiently cover the entire adult life of the animal to show changes in creatine content. Chanutin's conclusion regarding nitrogen content may be true in his experiments when whole, eviscerated animals were used. They are, however, in sharp disagreement with various other reports, particularly those of Bürger³⁵ and Hatai³³ who have analyzed individual tissues and report definite variations with age. A more recent report, differing from all these, is that of Asmolov,⁴⁰ who finds that as rabbits grow older the total nitrogen content of hydrolyzed muscle increases while the water content decreases. Hatai⁴¹ has also found this change in water content. His analyses cover less than one year of life, but show that during this time the per cent of solids reaches a maximum while the young are nourished by mother's milk. A more complete study of the water content is that of Lowrey⁴² who has analyzed various tissues of the rat for water during the first year of life. In general, his results indicate that most tissues show a progressive decrease in water content during this interval, the most rapid change taking place during the first four weeks. Lückner⁴³ found a massive increase in the iodine content of the blood of humans over 50 years of age.

Finally, a brief note by Hackh and Westling,⁴⁴ who suggest the possibility that old age may be caused by an accumulation of heavy water in the organism, may be mentioned. There are other papers in the literature on the subject, but they are mostly of the type reviewed here, and are, in general, marred by the same defects. It will be apparent that, while enough information has been gathered to show that some changes do occur during the life of an animal, there is disagreement among various investigators as to just what these changes are. And further, few, if any of the workers have carried out studies over the entire life span of any species. There is, therefore, need for a complete and careful study, particularly of water, nitrogen, and phosphorus, of individual tissues of animals over the entire lifetime from birth to advanced senescence.

The investigations reported herein are concerned wholly with the acid soluble phosphorus content of human tissues. Pectoral muscle, liver and kidney cortex were selected. The material was secured at autopsy. The first intention was to secure fresh material from normal subjects *immediately* after death from accident or suicide. Practical experience, however, soon demonstrated that this was not feasible. Consequently, the question of the extent of postmortem changes came under consideration. Experiments on dogs demonstrated that postmortem changes were confined to the free acid soluble phosphorus but did not affect the total acid soluble phosphorus.

In table 1 is shown the distribution of the subjects by age and cause of death. Analysis of any diseased tissue is always open to question. However, a comparison of the data in table 1 with those in table 2 did not show any significant effects of the various disease conditions on the content. It is possible that more data might make possible some such correlation but until additional information is available it is tentatively concluded that none of these pathological conditions significantly affect the content of total acid soluble phosphorus.

TABLE I
Causes of Death

	Prematurity	Accidents, unknown	Diseases of the brain	Diseases of the heart and blood vessels	Diseases of the lungs and respiratory tract	Diseases of the kidney	Diseases of the liver	Diseases of the blood	Carcinoma-tosis
until 14 da.	4				1			1	
until 6 mos.					3				
until 3 yrs.			1		5			1	
10-13 years			2	1		1		1	
20-30 years		5			1	1			
30-40 years		2	1	1	2	1		1	
40-50 years		2		1	2		1	1	
50-60 years			1	1	2	3			1
60-70 years		3	1	6	2		1		4
over 70 yrs.		1	1	3	2				1
Totals	4	13	7	13	20	6	2	5	6

METHOD OF ANALYSIS

The analyses were done by the following method⁴⁵:

A sample of tissue (1 to 2 gm.) was weighed, ground with sand, placed in a 20 c.c. graduated centrifuge tube, and water was added. The proteins were precipitated with 5 c.c. of 20 per cent trichloroacetic acid and the volume made up to 20 c.c. with water. After shaking and centrifuging, 2 c.c. of supernatant fluid were drawn off and heated with 0.1 c.c. concentrated H_2SO_4 . When a dark color appeared 3 drops of 30 per cent H_2O_2 (superoxol) were added. After complete decoloration the excess H_2O_2 was driven off by boiling three minutes with 5 c.c. of water. The clear solution together with washings was placed in a 25 c.c. volumetric flask; next 1 c.c. of molybdic acid solution and 2 c.c. of hydroquinone solution were added, and the contents mixed. After 5 minutes, 10 c.c. of $Na_2SO_3-Na_2CO_3$ solution were added for the development of the blue color. This mixture was then compared with a standard by colorimeter.

RESULTS

The results of these analyses are shown in table 2. In chart 1 the mean values, as shown in the table, are reduced to graphs which show very definite

trends. The values for muscle show a steady increase up to midlife and a steady decline after 40 years of age. Because of the wide range of values the data were subjected to statistical analyses by Fisher's formulae⁴⁶ and the validity of differences in mean values established. Compared to the early figures all values on the ascending limb of the curve are significant and likewise the differences between the apical values and those on the descending slope are significant.

The mean values for each sex cannot be interpreted separately since both the proportions and the absolute numbers are too variable in the different groups. In the two early groups the means for the females are much lower than for males but the ranges are comparable. In the next five age groups

TABLE II
Total Acid-Soluble Phosphorus Mg./100 gm. Dried Tissue

Age		Sex	Kidney	Liver	Muscle
<i>Up to 9 days</i>					
1	3 hours	F.	40	52	65
2	6 hours	M.	44	36	45
3	2 days	M.	79	56	61
4	2 days	M.	59	71	62
5	3 days	F.	58	68	89
6	9 days	M.	66	63	78
Mean			58	62	67
Standard deviation			13.58	7.13	13.67
Standard error			5.55	3.19	5.66
<i>Up to 6 months</i>					
7	2 months	M.	114	107	89
8	4 months	M.	75	83	91
9	6 months	F.	69	76	71
Mean			86	89	84
10	6.5 months	F.	81	90	84
11	7 months	M.	124	135	90
12	7.5 months	F.	120	121	88
13	13 months	M.	78	67	88
14	15 months	M.	82	96	100
15	1.5 years	F.	94	128	107
16	3 years	M.	120	110	108
Mean			100	113	96
Standard deviation			19.20	16.33	9.35
Standard error			7.26	6.67	3.82
<i>10-13 years</i>					
17	11 years	M.	120	103	100
18	12 years	M.	78	112	133
19	12 years	M.	104	106	93
20	12 years	F.	105	116	120
21	13 years	F.	103	91	113
Mean			102	106	112
Standard deviation			13.52	8.66	14.22
Standard error			6.05	3.87	6.36

TABLE II (Continued)

Age		Sex	Kidney	Liver	Muscle
<i>20-30 years</i>					
22	20 years	M.	122	120	160
23	21 years	M.	105	104	126
24	23 years	F.	106	115	130
25	28 years	M.	98	92	144
26	28 years	M.	93	122	145
27	29 years	M.	105	95	98
28	30 years	M.	96	104	115
Mean			104	107	131
Standard deviation			9.59	10.99	19.19
Standard error			3.92	4.16	7.25
<i>30-40 years</i>					
29	31 years	M.	98	106	117
30	31 years	M.	—	109	149
31	31 years	M.	102	105	128
32	32 years	M.	122	109	134
33	34 years	M.	100	(136)*	114
34	38 years	F.	100	103	145
35	39 years	F.	110	124	136
36	40 years	F.	89	97	138
Mean			103	108	133
Standard deviation			9.63	7.72	11.60
Standard error			3.64	2.92	4.10
<i>40-50 years</i>					
37	43 years	M.	104	107	137
38	43 years	F.	78	110	123
39	44 years	F.	111	119	124
40	45 years	M.	112	127	137
41	46 years	F.	126	134	150
42	50 years	M.	86	85	89
43	50 years	F.	91	109	96
Mean			101	118	134
Standard deviation			15.63	10.30	9.91
Standard error			5.91	4.21	4.43
<i>50-60 years</i>					
44	51 years	M.	86	84	90
45	51 years	M.	74	88	94
46	53 years	M.	102	130	124
47	53 years	F.	120	114	122
48	58 years	M.	88	92	102
49	59 years	M.	76	91	93
50	60 years	F.	89	116	—
51	60 years	F.	109	110	110
Mean			93	99	105
Standard deviation			15.52	12.50	14.01
Standard error			5.49	4.72	5.29

TABLE II (Continued)

Age		Sex	Kidney	Liver	Muscle
<i>60-70 years</i>					
52	61 years	M.	—	79	83
53	61 years	F.	89	106	—
54	62 years	F.	107	104	121
55	63 years	M.	80	125	120
56	64 years	M.	85	126	116
57	64 years	M.	99	109	117
58	64 years	M.	100	82	112
59	65 years	F.	99	114	131
60	65 years	M.	69	88	74
61	65 years	F.	116	124	120
62	65 years	M.	56	57	85
63	66 years	M.	68	57	100
64	67 years	F.	72	88	98
65	67 years	M.	68	75	101
66	67 years	M.	105	58	91
67	68 years	M.	90	100	110
68	68 years	F.	76	57	60
Mean			88	91	108
Standard deviation			15.18	24.08	14.00
Standard error			3.92	5.84	3.74
<i>Over 70 years</i>					
69	72 years	M.	103	100	102
70	72 years	M.	90	90	—
71	73 years	M.	70	60	88
72	73 years	M.	72	74	67
73	76 years	F.	43	69	66
74	85 years	F.	71	102	110
75	88 years	M.	80	83	92
76	90 years	F.	77	87	96
Mean			80	83	89
Standard deviation			11.23	13.79	15.50
Standard error			4.24	4.88	5.86

* Disregarded in calculating standard deviation and error.

the means are of the same order. In the last three the means for the males are approximately the same and definitely lower than for the females except in the last group. It is doubtful, however, if any significance can be attached to these differences.

The concentrations of total acid soluble phosphorus in the liver and kidney were of comparable orders with those for muscle up to three years of age. From that time on to 50 years there was no significant change in either. After that age the mean values decreased at about the same rate.

In none of the three tissues were the mean terminal values as low as the initial values. After the six month period the mean values for muscle were consistently higher than for the other tissues, those for the kidney consistently lower.

These results are not entirely in accord with those of another investigation in this laboratory on a colony of white rats. While these results will not be published until later it may be said that no consistent changes in the

content of acid soluble phosphorus were found in any tissue but muscle. In muscle the decrease in concentration began at a period much earlier in the life span than is the case in the human subjects. The reasons for these differences are not clear at present.

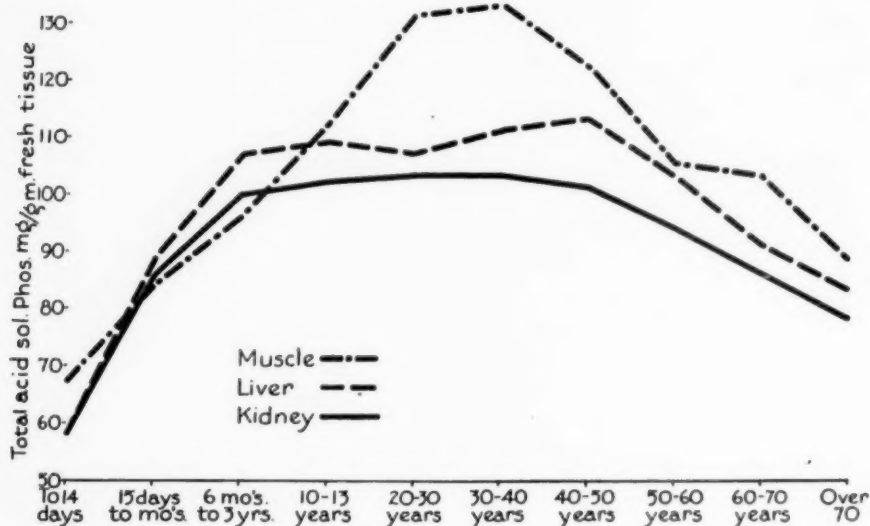


CHART 1.

CONCLUSIONS

1. Analyses for the concentration of total acid soluble phosphorus in muscle, kidney and liver tissue from 76 human subjects ranging in age from prematurity to 90 years have been made.
2. In muscle the mean concentration increased progressively to 30 years of age and decreased after 40.
3. In liver and kidney the mean values increased progressively to three years of age but remained fairly constant thereafter to 50 years, after which there was a progressive decline to 90 years.

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BIBLIOGRAPHY

1. STRUCK, H. C., and VISSCHER, M. B.: Studies on changes with increasing age in the phosphorus fractions of various tissues of the rat, *Am. Jr. Physiol. (Proc.)*, 1935, cxiii, 128.
2. BARTOLI, A. J., COHEN, J. L., and STRUCK, H. C.: A study of the total acid soluble phosphorus in skeletal muscle of rats, *Am. Jr. Physiol. (Proc.)*, 1937, cxix, 267.
3. PEARSON, P. B.: Inorganic phosphorus of horse serum: Effect of age and nutrition, *Jr. Biol. Chem.*, 1934, cvi, 1.

4. ELVEHJEM, C. A., and KLINE, B. E.: Calcium and phosphorus studies in the chick, Jr. Biol. Chem., 1933, ciii, 733.
5. VAN LANDINGHAM, A. H., HENDERSON, H. O., and BOWLING, G. A.: Composition of the blood of dairy cattle. I. The effect of age and phosphorus intake on calcium and phosphorus content of cattle whole blood, Jr. Dairy Sci., 1935, xviii, 557.
6. CURRADO, C.: L'Uricemia nell'et  senile, Boll. Soc. ital. biol. sper., 1929, iv, 9.
7. LESNE, E., ZIZINE, P., and BRISKAS, S. B.: Note sur les variations du cuivre dans le differents ages, Compt. rend. Soc. biol., 1936, cxxi, 1582.
8. ECK, M., and DESBORDES, J.: Influence de l'age sur les variations de la cholesterinemie et du pouvoir cholesterolytique, Compt. rend. Soc. biol., 1935, cxviii, 498.
9. KALABUKHOV, N., and RODIONOV, V.: Changes in the blood of animals according to age: Changes in the blood of rodents (*Mus musculus* L. and *Citellus pygmaeus* Pall.) and birds (*Passer montanus* L. and *Larus ribibundus* L.) during the period of growth, Folia Haematol., 1934, lii, 145.
10. KURADO, K.:  tudes sur la teneur en eau dans le sang de la souris au cours du developpement, Keijo Jr. Med., 1934, v, 140.
11. WATCHORN, E.: Normal serum calcium and magnesium of the rat: Relation to sex and age, Biochem. Jr., 1933, xxvii, 1875.
12. KIRK, E. W., LEWIS, W. H., and THOMPSON, W. R.: The effect of age on plasma calcium content of men, Jr. Biol. Chem., 1935, cxi, 641.
13. PARAF, J.: La glutathionemie et la s nilit , Ann. d. Med., 1935, xxxvii, 219.
14. PAGE, I. H., KIRK, E., LEWIS, W. H., JR., THOMPSON, W. R., and VAN SLYKE, D. D.: Plasma lipids of normal men at different ages, Jr. Biol. Chem., 1935, cxi, 613.
15. HELLER, V. G., and PURSELL, L.: Chemical composition of the blood of the hen during its life cycle, Jr. Biol. Chem., 1937, cxviii, 549.
16. HELLER, V. G., PAUL, H., and THOMPSON, R. B.: Changes in blood calcium and phosphorus partition during the life cycle of the chicken, Jr. Biol. Chem., 1934, cvi, 357.
17. ROCHE, J., and LEANDRI, A.:  tude quantitative de la phosphatase des os longs au cours de la croissance du rat, Compt. rendu Soc. biol., 1935, cxix, 1141.
18. BURNS, C. M., and HENDERSON, N.: The mineral constituents of bone. II. The influence of age on the mineral constituents of bones from kittens and pups, Biochem. Jr., 1936, xxx, 1207.
19. BLUME, H.: Chemische Untersuchungen  ber den Glykogengehalt und Gesamtkohlenhydratgehalt des menschlichen Herzens, Beitr. z. path. Anat., 1934, xciii, 20.
20. PEARCE, J. M.: Age and tissue respiration, Am. Jr. Physiol., 1936, cxiv, 255.
21. SEKLA, B.: Esterolytic processes and duration of life of *Drosophila melanogaster*, Brit. Jr. Exper. Biol., 1938, vi, 161.
22. FALK, K. G., NOYES, H. M., and SUGIURA, K.: Lipase actions of extracts of the whole rat at different ages, Jr. Gen. Physiol., 1925, viii, 75.
23. LEBENSOHN, E. G.: Beziehungen zwischen Alter, Zellstoffwechsel und Wachstumsgeschwindigkeit in vitro, Arch. exper. Zellforschung, 1934, xvi, 364.
24. DAVIS, J. E.: Effect of advancing age on the oxygen consumption of rats, Am. Jr. Physiol., 1937, cxix, 28.
25. STOLFI, G.: Ricerche sulla costituzione chimica del grasso del connattivosottocutanea dell'uomo. I. Acidi grassi liquidi e solidi nei varii periodi della vita, Boll. soc. ital. Biol. sper., 1935, x, 108.
26. TUNG-PI CHOW, and ADOLPH, W. H.: Copper metabolism in man, Biochem. Jr., 1935, xxix, 476.
27. ZONDEK, S. G., and KARP, J.: The relationship of iron with the ageing of cells, Biochem. Jr., 1934, xxviii, 587.
28. GREENBERG, D. M., and TUFTS, E. V.: Variations in magnesium content of the normal white rat with growth and development, Jr. Biol. Chem., 1936, cxiv, 135.
29. McCAY, C. M., TUNISON, A. V., CROWELL, M., and PAUL, H.: The calcium and phos-

- phorus content of the body of the brook trout in relation to age, growth, and food, *Jr. Biol. Chem.*, 1936, cxiv, 259.
30. WINTER, K. A.: Der Gesamtchloridgehalt neugeborener Ratten, *Biochem. Ztschr.*, 1934, cclxxii, 384.
 31. COLE, V. V., and KOCH, F. C.: A study on the phosphorus distribution in rat striated muscle as influenced by age, diet, and irradiated ergosterol, *Jr. Biol. Chem.*, 1931, xciv, 263.
 32. KOCH, W., and KOCH, M. L.: The chemical differentiation of the brain of the albino rat during growth, *Jr. Biol. Chem.*, 1913, xv, 423.
 33. HATAI, S.: Amount of non-protein nitrogen in the central nervous system of the normal albino rat, *Jr. Comp. Neur.*, 1917, xxviii, 361.
 34. EPELBAUM, S. E., KHAIKINA, B. I., and SKVIRSKAYA, E. B.: Effect of age on phosphorus compounds of the brain, *Ukrain. Biokhem. Zhur.*, 1936, ix, 613.
 35. BÜRGER, M.: Die chemischen Altersveränderungen im Organismus und das Problem ihrer normonalen Beeinflussbarkeit, *Verhandl. d. deutsch. Gesell. f. inn. Med.*, 1934, xlv, 314.
 36. KEUENHOF: Quoted by Bürger.³⁵
 37. MOULTON, C. R.: Age and chemical development in mammals, *Jr. Biol. Chem.*, 1923, lvii, 79.
 38. BERNSTEIN, FELIX: Growth and decay, *Cold Spring Harbor Symposia*, 1934, ii, 209.
 39. CHANUTIN, A.: The influence of growth on a number of constituents of the white rat, *Jr. Biol. Chem.*, 1931, xciii, 31.
 40. ASMOLOV, E.: Variations in nitrogen fractions and water content of rabbit muscles at different stages of growth, *Bull. biol. med., U. S. S. R.*, 1936, i, 119, 121.
 41. HATAI, S.: Changes in the composition of the entire body of the albino rat during the life span, *Am. Jr. Anat.*, 1917, xxi, 23.
 42. LOWREY, G. L.: The growth of the dry substance in the albino rat, *Anat. Rec.*, 1913, vii, 143.
 43. LÜCKER, H.: Kritik der Blutjodbestimmungs-methoden bei alkalischer und saurer Verbrennung, *Deutsch. Arch. f. klin. Med.*, 1933, clxxv, 681.
 44. HACKH, I. W. D., and WESTLING, E. H.: A possible cause of old age, *Science*, 1934, lxxix, 231.
 45. PINCUSSEN, L.: *Mikromethodik*, 155, 6th ed., 1937.
 46. FISCHER, R. H.: *Statistical methods for research workers*, 1928.

INFARCTION OF THE HEART. III. CLINICAL COURSE AND MORPHOLOGICAL FINDINGS*

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In the first two parts of this study the underlying conditions predisposing to cardiac infarction, and the symptomatology of acute attacks were presented. In this paper the course, common sequelae and morphological data will be discussed.

CLINICAL FEATURES AND COMPLICATIONS FOLLOWING INFARCTION

Congestive Failure. The very important part played by congestive failure after coronary thrombosis has been studied carefully by Master and his associates.²⁰ Evidence of "backward" failure appeared in the form of ankle edema in 55 per cent of these cases. In some it had been present before. In others death occurred before much failure developed. *Enlargement of the liver*, at times with ascites, was observed in 20 per cent of the small number of cases with data on this point. It was found relatively more frequently when the right ventricle was badly damaged, as noted by Libman,²¹ but also in cases where the left ventricle was the only part involved morphologically. *Jaundice* was found 11 times. In two cases an associated "alcoholic" cirrhosis, and in one case a stone in the ampulla of Vater were found. In the remainder passive congestion was present. Three had so-called "cardiac cirrhosis." In six cases infarcts of the lung were present. No patient survived an attack associated with jaundice.

Shock. A combination of the varied peripheral and central phenomena comprising the clinical picture of shock appeared in more than half of the cases. In others, though present, it was overshadowed by manifestations of congestive failure. It was often severe when pain was marked, but each appeared alone in some cases. The so-called characteristic facies of acute infarction is largely descriptive of clinical shock.

Extracardiac Embolism and Infarction. Embolism from dislodged mural thrombi is one of the unpredictable complications of cardiac infarction which makes prognosis doubtful. In table 1 are presented the data for embolism and infarction and the time after cardiac infarction at which embolism appeared. Careful study failed to reveal any clue by which it could be predicted that embolism would occur. No association was found with age, sex, blood pressure level, pain, use of digitalis or other factors. Approximately one-half of those with auricular fibrillation had mural throm-

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TABLE I
Peripheral Embolism and Infarction After Cardiac Infarction

Location	Embolus Derived From Mural Thrombus	Embolus Derived From Non-Cardiac Site	Infarct Without Local Arterial Damage or Mural Thrombus	Infarct Derived From Local Arterial Disease	Total
Lung	19	9 (Leg 3; Pelvis 1; ? 5)	15 (10 recent)		43
Kidney	20	2 (Bacterial endocarditis)	4 (old)	3	29
Spleen	13	1 (Aortic mural thrombus)	3 (old)		17
Brain	6			9(2 hemorrhage)	15
Femoral	5			3	8
Mesenteric	2			1	3
Carotid	1				1
	66	12	22	16	116

Embolism occurred 78 times in 60 cases

Time of Embolism After Cardiac Infarct

	Day													Week		Month		Total	Un-known
	4	5	6	7	8	9	10	11	12	13	14	3	4	2	3				
Number of Cases	1			3	2	2	1	2	2	1	2	6	9	2	3	36		30	

bosis, but it did not predispose unduly to dislodgment and embolism. It was found that embolism of cardiac origin was not usually fatal unless to the leg, brain or mesentery. Emboli from the right side of the heart were frequently present, but massive embolus occluding the lumen of the pulmonary artery was always derived from systemic veins. Pulmonary infarcts were most frequent in the lower lobes.

In this series cerebral vascular accidents following cardiac infarction were more frequently thrombotic, depending on local vascular fault, than embolic. It may be that the rapid fall in arterial tension after injury to the heart was enough to cause formation of a thrombus where disease was already present in the artery.

There were 15 cases of pulmonary infarction without any thrombus or embolus in the pulmonary arterial tree. These cases were invariably associated with marked left ventricular failure, stasis in the pulmonary circuit and pulmonary venous thrombosis. Such examples of cerebral and pulmonary infarction indicate that local vascular disturbances following cardiac infarction are responsible for a proportion of clinical phenomena which are often assumed to be embolic in nature. In addition, these findings might be taken to support the belief of an increased thrombotic tendency of the blood in coronary thrombosis. The earliest embolic accident occurred on the

fourth day after the acute cardiac lesion, but the majority appeared in the second, third and fourth weeks. A few cases met with the accident months after infarction.

PROGNOSIS

The likelihood of survival in any case of cardiac infarction depends on many different factors and unpredictable complications. Data on survival are recorded in table 2. Until a method is devised to forecast embolism,

TABLE II
Survival After Initial Attack

	Weeks						Months						Years							
	1	2	3	4	5	6	2	3	4	5	6	8	10	1	2	3	4	5	6	old
Number of Cases Dying Before End of Period Indicated	45	37	10	12	4	6	5	10	6	4	11	12	4	15	11	14	6	5	3	80

Survival After Acute Attack

Number of Cases Dying Before the End of Period Indicated	Days														Weeks			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	3	4	5	6
(114) First infarct.....	12	9	5	5	5	5	6	5	5	2	7	6	5	7	10	12	4	6
(67) Second infarct.....	10	3	4	4	5	3	7	1	4	2	2	1	2	3	7	4	2	3
Total.....	22	12	9	9	9	7	13	6	9	4	9	7	7	10	17	16	6	9

rupture and syncopal deaths, prognosis must rest on probability. If we assume the absence of complications, then indications of a large infarction are of grave significance. Clinically these are signs of either severe shock or congestive failure or both: namely, large heart, tachycardia, edema, both pulmonary and peripheral. Of the laboratory findings in uncomplicated cases a high fever, high leukocytosis with a shift to the non-filamented cells, rapid sedimentation rate, high non-protein nitrogen usually indicate a large area of damage. Electrocardiographic evidence of irregularities of rhythm and conduction defects is of more value prognostically than is the degree of T-wave change for this latter is not necessarily proportional to the damage to the heart. Pulmonary infarction or pneumonia adds to the gravity of the condition but are not necessarily fatal. Cases may end in recovery or death, quite contrary to all prognostic indications. The criteria of prognosis stressed in the literature are statistically valuable and show definite trends for groups of cases. Prognosis is the art of predicting the outcome of an *individual* case, however, and as yet no method or combination of methods exists by which accurate prophesy of final results can be made early in individual cases of infarction.

CAUSE OF DEATH

Seasonal variation in death rate for different conditions is a well-established fact. Figure 1 shows the relationship of acute attacks and deaths by season.* There is a constant increase from the low summer death rate through fall to the high winter and spring rates. In addition to the factors which govern seasonal changes in death rate from congestive failure and related conditions, a very important factor in this series is the

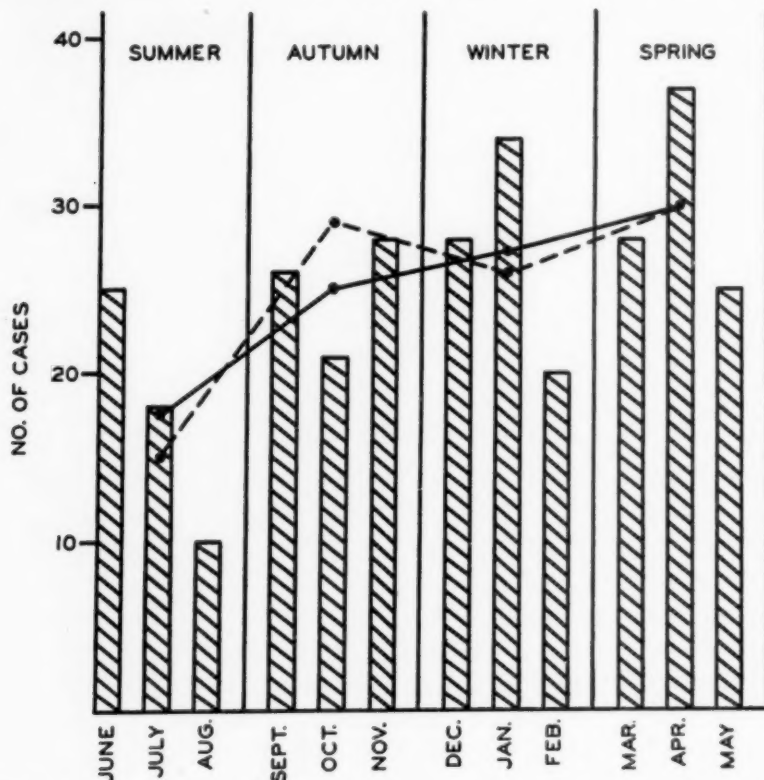


FIG. 1. Distribution of deaths by month and season. The unbroken line represents the percentage of deaths (300), the broken line represents the percentage of acute attacks (247) in each season.

seasonal difference in frequency of acute attacks. Since 166 cases died within a month of the acute episode, the seasonal incidence of deaths shows a close relation to the distribution of acute attacks.

Age at death for the whole group averaged only one year older than age at onset for those where date of onset was known. The charted distribution by decades superimposes almost exactly that for age at onset (see Part I). Because the survival period was unknown in so many cases with obviously old scars, the data for duration of life after infarction are incomplete and not accurate.

* For acute attacks by month see Part I, Am. Heart Jr., 1937, xiv, 684.

In table 3 are found the number of cases in which varied factors were the main or contributory *causes of death* in the groups of infarcts studied. The prime cause of death in this series was congestive failure, a point recently stressed by Master²⁶ and others. The next most frequent cause of death was collapse and shock. The mechanism of death in such cases of "dyskinetic" and "hypokinetic" cardiac failure has been admirably expounded by Harrison.¹²

Under the head of syncope are included all cases of instantaneous death where the victim literally dropped dead or died unexpectedly with symptoms lasting too short a time for any observations to be made. In addition, five cases found dead in bed were probably similar. No case with embolism had such a death, nor was there any case where death followed coronary thrombosis in less than one hour and a quarter. Unpredictable sudden death has long been known as a frequent associate of angina pectoris and coronary thrombosis. The mechanism has been explained variously: by Allbutt as due to vagal inhibition and ventricular standstill, by Hering as ventricular fibrillation, by Leary as "coronary spasm" and by Levy as "acute fatal coronary insufficiency" without spasm. Each of the above speculations apparently assumes that the cause of death is something which, interfering with the cardiac mechanism, effects a condition of actual or functional asystole. It would be expected that ensuing manifestations would be those of cerebral anoxemia, particularly respiratory effort and such changes as occur in the asystolic phase of an Adams-Stokes' attack. From the meager information available it is found that in the instant deaths in this series there was a total cessation of "vital" functions as a precipitously occurring syncope, irrevocable in nature.

In a study of syncope Weiss⁴³ has suggested that the tendency to fainting may become enhanced as a conditioned reflex. In addition, he has demonstrated that fainting and convulsions may be produced in one form of carotid sinus syncope without the intermediation of cardiac or depressor reflexes, being a purely cerebral reflex.⁴² With these points in mind a careful study of the past history and clinical course of these cases was undertaken. Seventeen of the 29 cases of sudden death had a history of some form of fainting or syncopal attacks prior to infarction. The group with syncope had a greater liability to sudden death than the groups with angina pectoris, hypertension, congestive failure or the various types of conduction defects. On the basis of these facts we wish to emphasize the abrupt and apparently simultaneous cessation of the functions of heart beat, respiration and consciousness as a "totalitarian" form of death frequent after cardiac infarction, cerebral in origin, evidently depending on reflexes from the damaged heart, rather than asystole per se.

There were cases without embolism or rupture where the heart beat was undetectable clinically and death followed minutes after the first sign of air hunger, intense respiratory effort and cyanosis, usually with some convulsive

TABLE III
Cause of Death

	Old Cases		Old and Recent		Recent		Total		Total
	Main	Con- tribu- tory	Main	Con- tribu- tory	Main	Con- tribu- tory	Main	Con- tribu- tory	
Cardiac									
Congestive failure.....	52	18	25	40	28	50	105	108	213
Pulmonary edema.....	3	46	2	48	4	61	9	(155)	(164)
Cardiac cachexia.....	5	4	1			1	6	(5)	11
Rheumatic heart disease....	2	4		2	1		3	(6)	9
Bacterial endocarditis.....		1				4		5	5
Paroxysmal tachycardia....				2		2		4	4
Digitalis poisoning.....		1				1		2	2
Total.....	62		28		33		123	119	242
Shock									
Collapse and shock.....		13	12	14	32	23	44	50	94
Syncope; sudden death.....	5		12	2	12	3	29	5	34
Rupture.....			4*		14		18		18
Total.....	5		28		58		91	55	146
Vascular									
Embolism.....	9	12	6	21	6	24	21	57	78
Cerebral vascular accident..	11	9	3	1	3	2	17	12	29
Gangrene of leg.....	3	3			1	1	4	4	8
Mesenteric thrombus.....	1			(1)†	(1)†		1(1)	(1)	(2)1
Total.....	24		9		10		43		116
Infection									
Bronchopneumonia.....	2	22		7		17	2	46	48
Syphilitic aortitis.....		3		2		5		10	10
Lobar pneumonia.....	4		1	2			5	2	7
Empyema.....	1	1	1	1	1	2	3	4	7
Sepsis.....		4				3		7	7
Cholecystitis.....		3		3		1		7	7
Tuberculosis.....	2	1		1			2	2	4
Urinary tract infection....		1		1		2		4	4
Erysipelas.....	1						1		1
Peritonitis.....			1				1		1
Purulent pericarditis.....			1				1		1
Total.....	10		4		1		15		91

* 1 Traumatic. † Embolus.

TABLE III.—Continued.

	Old Cases		Old and Recent		Recent		Total		Total
	Main	Con-tributory	Main	Con-tributory	Main	Con-tributory	Main	Con-tributory	
Miscellaneous									
Diabetes.....	2	3	1	4	5	4	8	11	19
Operations.....	3	1	3		5	1	11	2	13
Uremia.....	3	2		3		2	3	7	10
Peptic ulcer.....		4	1	2	1	2	2†	8	10
Trauma.....		1	1	1		1	1	3	4
Hemorrhage.....				1		2		3	3
Carcinoma.....	1	2					1	2	3
Alcoholic cirrhosis.....		2		1				3	3
Hodgkin's disease.....	1						1		1
Lymphoid leukemia.....					1		1		1
Hemochromatosis.....		1						1	1
Partial coarctation of the aorta.....						1		1	1
Total.....	10		6		12		28		

† Rupture.

movements. Apparently these cases were *primarily* due to some form of cardiac standstill.

Embolism was the direct cause of death in 21 cases and contributed in many more. The only cases where it was rapidly fatal were those with massive pulmonary embolus from a systemic vein. All of these survived for at least ten minutes, and many for hours after the first symptom.

Many other factors listed in the table are self-explanatory in their rôle as lethal agents.

MORPHOLOGICAL CONSIDERATIONS

The fundamental principles of the structural changes in cardiac infarction have been understood since they were enunciated by Weigert⁴¹ and Ziegler.⁴⁶ Certain obscure points still exist, and others are found which may be elucidated by statistical presentation.

Location of Arterial Damage and Infarction. There is still some disagreement in the literature regarding the prevalence of involvement of different arteries. The early reports of Wearn⁴⁰ and Levine¹⁷ revealed a great preponderance of lesions of the left anterior descending artery. In subsequent studies Parkinson and Bedford³² and Barnes and Ball³ have found a different distribution, and the latter writers concluded that designation of the left anterior descending branch as "*the* artery of coronary occlusion" was no longer justifiable. Some of the reported groups have

TABLE IV
Arterial Distribution

Author	Left Anterior Descending	Right Main	Left Circumflex	Left Main	Miscellaneous	Total Lesions	Number of Cases
This series.....	242	60	55	13		370	287
Appelbaum and Nicolson.....	85	29	8	7	16	145	113
Parkinson and Bedford.....	24	18	10	3		55	55
Barnes and Ball.....	28	20	17			65	49
Levine.....	39	2	4		1	46	46
Lisa and Ring.....	22	4	1			27	24
Wearn.....	16	1	1		1	19	19
	456 (77%)	134 (23%)	96 (16%)	23 (4%)	18 (3%)	727	593

been tabulated and compared with this series in table 4. In the combined groups more than 75 per cent of all cases had a lesion of this artery and, in this series, 84 per cent of cases. Furthermore, as table 5 shows, the right coronary tree was involved seriously in only 21 per cent of the 287 cases.

TABLE V
Distribution of Arterial Lesions

Artery		
Left anterior descending chief lesion.....		178
Right main.....		16
Left circumflex.....		14
Left anterior descending and left circumflex.....		12
Left main.....		10
Left main and right main.....		8
Left anterior descending narrow right main thrombosed.....		8
Right main and left circumflex.....		7
Left anterior descending narrow, left, circumflex thrombosed.....		5
" " " thrombosed, right main narrow.....		5
" " " " and left circumflex narrow.....		4
" " " left circumflex narrow.....		4
" " " narrow, right main narrow and left circumflex narrow.....		3
Right main and left circumflex.....		3
Left main and left anterior descending.....		2
Right main and left main narrow.....		2
Right descending; left anterior descending and left circumflex narrow; right and left main and left circumflex. Left anterior descending narrow, right main and right descending thrombosed; intraventricular branch of left anterior descending; right main and anterior descending thrombosed and left circumflexed narrow—1 each.....		6
		287
Left anterior descending.....	242	
Left circumflex.....	55	
Left main.....	13	
Right main.....	56	
Right descending.....	4	
Left coronary tree.....	270	Right coronary tree..... 60
No artery.....	5	? 8

This information substantiates the impression that the left coronary artery, particularly its anterior descending branch, is the most prominently involved artery in infarction. A cause for this peculiar liability has been advanced by Lewis¹⁹ as due to "the relatively more exposed position" of the artery.

Whitten ⁴⁴ demonstrated that muscular branches supplying the left ventricle leave the parent stem at right angles to enter the muscle directly. This anchoring is said to cause buckling of the main artery between fixed points, favoring local damage. One might, therefore, expect more frequent damage to the left circumflex artery than is known to occur.

In the great majority of cases there was involvement of more than one artery or branch in the damaging changes leading to infarction. This is in general agreement with Saphir and his coworkers' observation of multiple lesions in the artery in every case in their study. There were some notable exceptions: In eleven cases there was no damage at all in the right coronary artery but only in the anterior descending branch of the left coronary, and in one case two infarcts had occurred with only this artery involved. Examples of isolated damage to the left circumflex or right main artery also appeared, but these cases were in the minority.

There was fairly close agreement between artery involvement and the location of myocardial infarction. Table 6 gives the distribution of gross

TABLE VI
Site of Infarct

	Single	Multiple	Total
Anterior apical region of left ventricle; right ventricle little involved...	91	30	121
Anterior apical region of both ventricles and intraventricular septum...	51	26	77
Posterior basal region of left ventricle.....	20		20
Anterior basal region of left ventricle.....	7	6	13
Lateral region of left ventricle.....	9		9
Lateral and posterior region of left ventricle.....	7	2	9
Anterior region of right ventricle.....	6	2	8
Anterior and lateral region of left ventricle and septum.....		7	7
Posterior apical region of left ventricle.....	5	1	6
Anterior and posterior region of left ventricle and septum.....		5	5
Posterior basal region of left and right ventricle and septum.....	2	3	5
Anterior and lateral region of left ventricle.....	1	1	2
Anterior and lateral and posterior region of left ventricle.....	1	1	2
Anterior and post-apical region of left ventricle and posterior base of left ventricle.....		2	2
Anterior basal region of right ventricle.....	1		1
Anterior basal region of left ventricle and all of right ventricle.....		1	1
Anterior apical region of left ventricle and lateral aspect of rt. vent.....		1	1
Anterior apical region of left ventricle and anterior aspect of rt. vent.....		1	1
Anterior apical region of left ventricle and anterior basal aspect of left ventricle.....		1	1
Papillary muscles alone.....	2		2
Papillary muscles and anterior apical region of left ventricle.....	2		2
Papillary muscles and posterior basal region of left ventricle.....	2		2
Papillary muscles and posterior basal region of right ventricle.....	1		1
Papillary muscles and anterior apical region of right ventricle.....	1		1
Papillary muscles and posterior basal region of left ventricle and lateral aspect of left ventricle.....	1		1

Left ventricle involved in 287 cases
 Septum 111
 Right ventricle 95
 Papillary muscles 10
 Auricle 3

TABLE VII
Location of Infarct

Author	Anterior and Apical Portion of Left Ventricle	Lateral Region of Left Ventricle	Posterior Basal Region of Left Ventricle	Right Ventricle	Miscellaneous	Total
This series	223	30	43	9	25	300*
Appelbaum and Nicolson	91	10	16	0	10	118
Barnes and Bell	28	8	24	0	3	63
	342 (71%)	48 (10%)	83 (17%)	9 (2%)	38 (8%)	481

* Many of the cases with multiple infarcts in this series had both infarcts in the same general location.

lesions as described in the protocols. In a few cases the location was atypical, but the larger number of cases fell into one of the three groups illustrated by MacCallum.²⁴ In 72 per cent of all cases the lesion was located in the anterior apical part of the left ventricle, frequently with some involvement of the right ventricle and septum.

Recently Saphir and his coworkers³⁵ have reported observations on carefully dissected hearts with coronary artery lesions, citing some cases where a fresh infarct was not in the area supplied by a recently thrombosed artery. The infarct was in the region normally supplied by a previously obstructed artery, but the collateral supply had been taken over by the branch whose final obstruction resulted in a kind of "ectopic" infarction. There were nine cases in this series which can be explained on this basis (see table 8).

TABLE VIII
Infarcts Not in Area of Recent Thrombus

Fresh thrombus of left anterior descending, old occlusion of right main and infarct chiefly posterior and in right ventricle	3
Fresh thrombus of left anterior descending, narrow left circumflex, fresh infarct in lateral area of left ventricle	1
Anterior apex left ventricle, old scar and fresh thrombus in recanalized left anterior descending, old occlusion of left circumflex, fresh infarct in lateral and posterior left ventricle	1
Left circumflex fresh thrombus, infarct in anterior apex of left ventricle with narrow left anterior descending	1
Right coronary fresh thrombus, infarct in anterior apex of left ventricle especially system where left anterior descending is narrow	1
Old thrombus of left anterior descending, right main narrow, old scar at base posteriorly chiefly in area of supply of right main	1
Left anterior descending narrow, old scar in area, and fresh thrombus. Right main complete old occlusion. Left circumflex narrow, fresh infarct lateral left ventricle	1

Coronary occlusion or thrombosis and myocardial infarction are not identical and they do not follow invariably as cause and effect. Either may occur without the other. It is probable that the process of infarction differs in occlusive and constrictive arterial lesions. Table 9 gives the cases where

TABLE IX

Location of Infarcts Without Complete Occlusion of Artery

<i>Left anterior descending narrow—no occlusion</i>	
Old scar anteriorly and apex of left ventricle	32
Fresh infarct anteriorly and apex of left ventricle	15
Old scars with evidence of recanalization	8
Old scar and recent infarct anterior apex of left ventricle	1
<i>Left anterior descending narrow, right main narrow</i>	
Old scar anterior apex of left ventricle	1
Fresh infarct anterior apex of left ventricle	1
Old scar anterior apex of left ventricle and fresh posterior basal of left ventricle	1
<i>All arteries sclerotic and narrow</i>	
Posterior base of left ventricle and septum, old	3
Posterior base of left ventricle and septum, recent	1
Anterior right and left ventricle and septum—old and recent infarct	1
Anterior apex of left ventricle, posterior basal of left ventricle	1
<i>Left circumflex narrow</i>	
Two old scars in lateral wall of left ventricle	1
Number of infarcts and scars without complete occlusion	58

infarction occurred without a complete obstruction in the artery but where fibrotic narrowing, calcification, atheromatous abscesses or partial thrombosis produced permanent decrease in caliber of the artery. Approximately 20 per cent of the infarcts in this series were of this type. In these cases a careful search had been made for thrombosis of the artery leading to the infarct and none was found.

In some of these cases it is probable that myocardial damage followed *pari passu* the gradual narrowing of the arterial lumen as a so-called chronic infarct developed. Some of the silent infarcts were of this type. There were cases of acute infarction, however, easily recognized clinically as typical "coronary thrombosis," where myocardial infarction had occurred without any acute morphological change in the artery. Spasm was structurally impossible in these calcified and constricted coronaries. The pathogenesis of this type of infarct is unknown. No systematic study has been made of the coronary veins in these cases. In many individuals congestive failure was marked. It is recognized that coronary venous thrombosis may cause a clinical picture characteristic of coronary artery thrombosis³¹ with morphological changes in the heart, while in other cases the heart may show no damage.³² The suggestion is made that a combination of decreased arterial supply plus the increased venous pressure and stasis in the coronary veins, with or without venous thrombosis, may result in characteristic morphological infarction.

Of the five cases with normal arteries and no thrombus or embolus, one was an example of syphilitic occlusion of the mouth of a coronary artery. One was an infarct of a hypertrophied papillary muscle in an enlarged heart with mitral stenosis of rheumatic origin. In two cases perfectly normal arteries led to an infarct in the anterior apical region of the left ventricle.

There was one case of an old aneurysm with extensive adhesions and calcium in the scar but normal arteries were found. In the last four cases diligent search revealed no cause in the arteries for the myocardial lesions found. That coronary spasm may be sustained long enough to result in infarct is conceivable, but again the possibility of venous stasis and thrombosis seems a preferable speculation.

Coronary Anomalies. A few cases in this series had unusually located arteries with arteriosclerotic lesions and thrombosis. These are outlined in table 10. In all cases where an artery was abnormally placed structural changes had occurred.

TABLE X

Coronary Anomalies

Right coronary double with occlusion of branch which supplies anterior right and left ventricles and septum instead of normal left anterior descending	2
Division of left anterior descending into a right and left branch at its origin:	
Old infarct at base, fresh infarct at apex, anterior; old thrombus in right branch, fresh in left	2
Old infarct at base in anterior part of left ventricle, and occlusion of right branch	1
Infarct at apex of left ventricle and occlusion of left branch	1
Aneurysm of left branch and thrombus with infarct at anterior and apex of left ventricle ..	1
Anomalous course of left circumflex with occlusion	1
(Partial coarctation of aorta—1 case)	

In one of the cases where the left anterior descending branch was double, a small (5 to 6 mm.) aneurysm of the coronary artery was the site of thrombosis and infarct. There was microscopic evidence of degenerative changes in the artery but no evidence that the nature of the process was mycotic.

Heart Weight. Cardiac hypertrophy is frequently associated with hypertension, angina pectoris and congestive failure, as well as symptomless coronary disease. The literature stresses enlargement of the heart in cases of thrombosis^{40, 17, 32} (figure 2.) In addition, Bartels and Smith⁴ have alleged coronary thrombosis as a cause of hypertrophy without these other factors. In this series it was impossible to find many cases in which one factor alone was present. Table 11 gives the average weights of hearts in different categories. Using 350 and 400 grams as the upper limit of normal

TABLE XI

Heart Weight

Number	Range grams	Average grams
Men (205)	280-830	531
Women (90)	260-720	468
Hypertensives (137)	290-830	542
Hypertension not demonstrated (158)	260-800	480
Failure; no hypertension (25)	280-800	436
No failure or hypertension (8)	280-540	414
Total 295	260-830	512

for hearts in women and men, respectively, it was found that 83 per cent of women and 83.4 per cent of men had hearts heavier than normal.

The known hypertensives had hearts averaging 62 grams heavier than the rest of the cases. In the eight cases where no hypertension or failure had been present the average heart weight was only 414 grams, but two of

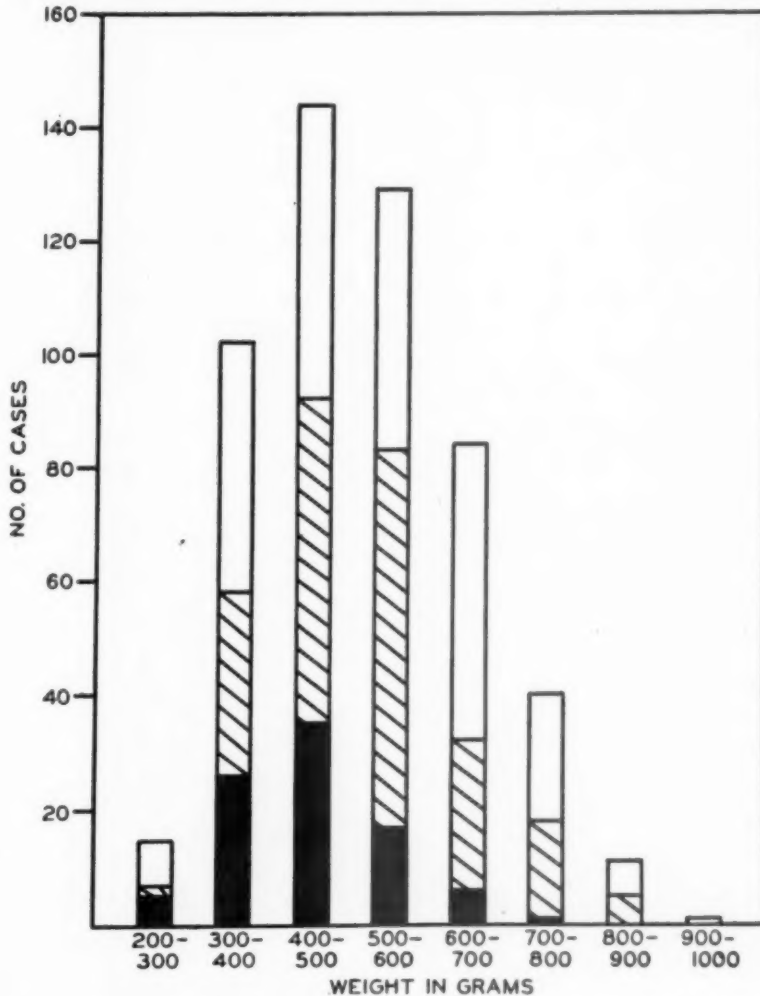


FIG. 2. Heart weight. Solid represents females, cross-hatched represents males in this series. The unmarked groups are additional cases from the literature.

these weighed more than 500 grams. Clinical evidence that the post infarction heart may not be enlarged is found in Palmer's report²⁹ that 36 per cent of cases surviving three months or more did not have clinically detectable enlargement. The conclusion seems justified that the majority of cases dying with cardiac infarction have enlarged hearts.

Intracardiac Mural Thrombi. Corvisart¹⁰ was one of the first to note the occurrence of intraventricular mural thrombi, but their significance was not comprehended until the pathology of infarction was better known. Reports of the incidence of mural thrombosis after infarction give widely divergent figures. For example, Parkinson and Bedford found only 14 instances in 83 cases, while Levine found 38 in his series of 46 cases. Comparison of several series is given in table 12, where it is found that 45 per cent of 698 cases had antemortem clots in the ventricle. The exact localization of mural thrombi and related data from the present series are outlined in table 13. The location followed the general distribution of infarcts. The septum was involved in slightly more than half of the cases in this series and embolism was abnormally frequent when a thrombus was attached to

TABLE XII
Intraventricular Thrombus After Infarction

Author	Number of Cases	Cases with Ventricular Thrombi	Per Cent
This series.....	300	142	47
Appelbaum and Nicolson.....	150	81	54
Lisa and Ring.....	100	34	34
Parkinson and Bedford.....	83	14	17
Levine.....	46	38	83
Wolff and White.....	19	7	37
	698	316	45

the septum. Emboli to the lungs occurred in 75 per cent of cases of right ventricular thrombi, but emboli were detected in only 34 per cent of cases where the thrombus was in the left ventricle.

Formation of mural thrombi is facilitated by early cessation of active muscular contraction in the infarcted area of the ventricle. In addition, when the infarct reaches the endocardial surface fibrin and exudate soon form. Rarely a mural thrombus may occur in a heart with marked coronary sclerosis and no gross infarct, though no such case was found in this series.

The fate of thrombi in cases which survive for long periods cannot be known surely until *intra vitam* diagnosis of mural thrombus is possible. A certain proportion are dislodged and become emboli. Some are gradually organized, especially if a large part of the underlying muscular tissue survives. There were 12 instances of old cardiac scars (with no mural thrombi) associated with peripheral infarcts where there was no local arterial disease. It seems reasonable to suppose that these were embolic in origin with perhaps dislodgment of the whole thrombus. There were cases with mural thrombi adherent to three year old scars of ventricular infarcts. Some of these had been covered by endothelium and had liquid centers.

Mural thrombi may interfere with normal cardiac function by mechanical interference with blood flow. There were such cases where several

chambers had large thrombi, and one case where a massive antemortem thrombus almost filled the entire left ventricular cavity.

Data indicating the length of time necessary for the formation of mural thrombi, after infarction, are found in table 13. There were three who died within 24 hours after infarction and who had early mural thrombi. Thrombi were uncommon until the fourth day, after which they became increasingly frequent among cases dying within the first month after infarc-

TABLE XIII
Intracardiac Mural Thrombi

Location	Number of Cases
Left ventricle alone	102
Both ventricles	15
Right auricle	8
Left auricle and left ventricle	7
Right ventricle alone	6
Right auricle and left ventricle	5
Left auricle alone	3
Both auricles and left ventricle	3
Both auricles and both ventricles	2
Left auricle and both ventricles	1
Right auricle and right ventricle	1
	(51%) 153

Left ventricle involved 135 times (7 multiple)
 Right " " 25 "
 " auricle " 19 "
 Left " " 16 "
 Septum " " 72 "

Multiple infarcts 34
 Old " 49
 Recent " 70

Time of Death After Infarction in Those With and Without Mural Thrombi

	Day							Week			Month		Old
	1	2	3	4	5	6	7	2	3	4	2	3	
Cases with mural thrombi	3	2	2	5	2	4	8	27	15	12	11	5	57
Cases with no mural thrombi	19	10	7	4	7	3	5	25	2	4	9	5	43

tion. Table 13 should be compared with table 1, which gives the date of embolic accidents.

Ventricular Aneurysm. Though the early pathologists (Morgagni) did not distinguish clearly between cardiac dilatation and aneurysm, Bérard⁶ noted the latter. The incidence of ventricular aneurysm in any series varies with the assiduity of the pathologist, the criteria employed and the proportion of very recent cases included. The last two factors doubtless account for the disparity of 5 per cent (Lisa and Ring) and 38 per cent (Appelbaum

and Nicolson) in reported studies. In this series cases with a definite localized margin and diameter of 3 cm. were included. It was found that 10 per cent of all cases with infarction developed aneurysmal dilatation, and 14 per cent of cases surviving a month or more did so. It could not be shown that sex, age, hypertension or other factors predisposed to aneurysm. Aneurysm appeared proportionally in cases of constrictive and of occlusive coronary lesions. Thickness of the wall was not necessarily a factor because in some cases aneurysm appeared when the wall was 5 mm. thick, and in

TABLE XIV
Ventricular Aneurysm

Author	Number of Cases	Number of Aneurysms	Per Cent
This series.....	300	31	10
Appelbaum and Nicolson.....	150	57	38
Lisa and Ring.....	100	5	5
Parkinson and Bedford.....	83	5	6
Levine.....	46	3	7
Wolff and White.....	19	3	16
	698	104	15

TABLE XV
Aneurysm of Ventricle
31 cases

<i>Artery Involved</i>		
Left anterior descending.....		28
Right main.....		1
?.....		2
<i>Location</i>		
Anterior apex of left ventricle.....		22
" " " " " and septum.....		4
Posterior " " " " " ".....		3
Anterior base " " " ".....		1
" apex of right and left ventricle.....		1
<i>Survived</i>		
Year or more.....		19
6-8 months.....		2
2-3 months.....		4
4-6 weeks.....		2
28, 26, 22, 17 days (1 each).....		4

some cases of scar 1 to 3 mm. thick no bulge had occurred. Old pericardial adhesions appeared in 16 cases, mural thrombi in 23. Location followed the pattern for the whole group. Though 16 had multiple infarcts, in only three did aneurysm arise from the second infarct. Half of the cases lived a year or more after the infarct which produced the aneurysm and five died of unrelated non-cardiac complications.

Formation of aneurysm has been demonstrated by roentgen-ray within six to seven days after infarct formation by Shookhoff and Douglas.³⁷ The earliest case in this series had an aneurysm 17 days after infarction, and there were three additional cases within four weeks. Clinical diagnosis of this condition was not made in the present series. Signs as described in

these cases followed no characteristic pattern and were not different in essentials from cases without aneurysm. Some clinical signs have been described by Libman²¹ and Medlar and Middleton.²⁷ Roentgen-ray studies, especially fluoroscopic or roentgen-kymographic, seem most likely to be of value in distinguishing these cases from (1) enlarged or dilated hearts and (2) pericardial effusions. This is not merely an academic point because one case in this series died due to laceration of the aneurysm by the needle at an attempted paracentesis for pericardial effusion. In extenuation it must be said that some clear fluid had been withdrawn, so a small pericardial effusion complicated the picture. If routine roentgen-ray studies were made in all cases of infarction, aneurysms would probably be detected in a larger percentage and at an earlier time than is commonly believed. Such a procedure is not justifiable, however, unless an acute problem in diagnosis arises.

Calcification of the Infarct. Hirschboeck¹³ has recently considered the infrequent finding of calcification of the myocardium after coronary occlusion and has cited the literature. In the present series extensive calcification of scars occurred in three cases. Two of these had aneurysm and old mural thrombi. One without aneurysm had old pericardial adhesions, as did one case with aneurysm. The average heart weight was 535 grams. One case survived four years, another one year, and the third for an unknown period. No roentgen-ray studies were made and the diagnosis was not suspected during life.

Spontaneous Rupture of the Ventricle. Fascination with the dramatic episode of rupture of the heart has outweighed accuracy in observation in the very numerous case reports appearing in the earlier literature. Recently several excellent reports have appeared, notable among which are those of Krumbhaar and Crowell¹⁵ supplemented by Davenport¹¹; Beresford and Earl⁷ and Benson, Hunter and Manlove.⁵ Incidence in postmortem studies varies with the type of material analyzed. The data on pertinent facts regarding rupture are found in table 16. It occurred in about 6 per cent of cases of infarction.

Little information is available concerning the time interval between infarction and rupture in reported cases. In a number of reports it appears that the episodes of infarction and rupture have been confused. The widely accepted belief that rupture occurs most frequently from the fifth to fourteenth days is based on Levine's¹⁷ nine cases. When the cases in this series and in his are compared, considerable differences are seen and it is found that most occurred in the first eight days with no special preponderance. Practically all did occur within two weeks of infarction. The earliest appeared 14 hours after the first symptom of pain in a previously asymptomatic woman of 47. The latest was 16 days after infarction. Before conclusions are drawn as to the time of rupture, more data should be gathered.

In this series there were nine women and eight men with cardiac rupture. Some form of arrhythmia was present in seven. No unusual association was found with hypertension, angina, failure or other conditions. Mural

TABLE XVI
Spontaneous Rupture of Ventricle

Artery Involved		Site of Rupture	
Left anterior descending	13	Anterior apex of left ventricle	12
Left circumflex	2	Lateral apex of left ventricle	2
Right main	2	Posterior base of left ventricle	2
		Septum	1

Heart Weight							
2-300	3-400	4-500	5-600	6-700	7-800	840 with pericardium	
1	6	4	3	1	1	1	

Time of Rupture After Infarction

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	?
Number of cases this series ..	1	3	1	2	1		3	1				2	1			1	1
Number of cases Levine		1			1	1	1	2						2			
Total	1	4	1	2	2	1	4	3				2	1	2		1	1

Incidence of Rupture

	Cases of Infarction	Number of Ruptures	Per Cent
This series	300	17	6
Appelbaum and Nicolson	150	9	6
Lisa and Ring	100	0	0
Parkinson and Bedford	83	5	6
Levine	46	9	20
Wolff and White	19	0	0
	698	40	6

thrombi were found in eight. The heart weight varied from 260 to 750 grams, the average, 588 grams. Whenever the record included observations on the circumstances immediately preceding rupture some form of activity was found. This varied from animated conversation to falling out of bed.

Survival after rupture fell into four periods. Two cases died instantaneously. They were probably similar to the sudden syncopal deaths without rupture. The nine cases where death occurred in a few minutes had signs of cardiac tamponade, acute "inflow stasis," sudden venous engorgement, cyanosis, severe respiratory embarrassment and other evidence of cerebral anoxemia. Survival lasted one to three hours in five cases. They had smaller tears in the heart and their ultimate death was also due to tamponade, though the disaster was not so rapidly lethal. The one case surviving eight days deserves particular attention because of the rarity of cases with this long survival. Classical infarction occurred while the patient, a 69 year old Russian Hebrew, was resting at night prior to bedtime, with crushing pain radiating down the left arm. This lasted six hours. Progress thereafter was uneventful until the fourth day, when in the hospital

sudden collapse occurred. There was gradual but only partial recovery and for eight days the patient suffered with increasing signs of congestive failure and finally died. At autopsy the heart was closely adherent to the pericardium, attached by means of a thick clot of organizing blood. A smooth rupture 3.5 by 3 cm. along the lateral margin of the left ventricle was in communication with a narrow sinus in the organizing tissue. The specimen weighed 840 grams. The tear was considered to be about a week old, with evidence of healing and endothelialization.

Embolism of a Coronary Artery. A critical review of coronary embolism has recently been made by Saphir.³⁴ The rarity of authentic cases is noted. In four cases in the present series coronary embolism from friable valvular vegetations seemed certain and in an additional case it is probable that an older embolism had caused infarction. Data on these cases are found in table 17. Contrary to Saphir's finding, sudden death did not occur,

TABLE XVII
Coronary Embolism

Number	Age	Sex	Pain	Failure	Heart	E. K. G.	Survival	Valves Involved	Artery	Heart Weight grams	Other Embolic Manifestations
1	78	F	Epigastric left arm	Slight	E	S. A. Tachycardia 136	16 days-rupture	Soft friable vegetation on aortic leaf of mitral	Left circumflex	260	0
2	69	M	Left shoulder Left arm	Moderate	E		12 days	Fungating vegetation on mitral	Left anterior descending (with some sclerosis)	520	Spleen Kidney
3	50	M	Substernal Left arm	0		"Coronary disease"	3 hours	Aortic stenosis with vegetation	Left anterior descending	480	7
4	35	F	Chest	0	E		12 hours	Aortic cusps crumbly vegetation	Right main	310	Spleen
(?)	65	F	Substernal	Slight			old?	Mitral valve Friable vegetation	Left anterior descending (some sclerosis)	335	Brain Kidney Mesentery

though one case died in three hours and one in 12 hours after the accident. These cases were not studied carefully clinically because those surviving the first day were moribund on admission. If the diagnosis in the questionable case be correct, it indicates that coronary embolism is not necessarily fatal. In this connection it should be noted that four of the five cases were over 50. The two youngest cases died soon after embolism occurred. Every case had some coronary sclerosis and presumably had developed collateral circulation. This is in agreement with Gross' belief in the increased efficiency of collateral circulation in older individuals.

Auricular Infarcts. It is improbable that the rarity of reported cases of infarction of the auricle is a true indication of its incidence. There were

two definite cases in this series and one additional case of a small scar in the auricular appendage in a case of syphilitic infarct of left ventricle. Clowe and his associates⁹ reported a case of rupture of the right auricle and analyzed the literature on auricular rupture, which revealed that the right auricle was perforated over twice as frequently as the left, in sharp contradistinction to the localization in ventricular rupture. In this series one clear cut case showed perforation occurring in the left auricle with especially prominent subepicardial necrosis, along with an embolic infarct of the left ventricle with final rupture. No auricular thrombi were found. In the other case the right coronary was the site of a completely occluding thrombosis and there was an infarct in the posterior basilar aspect of the right and left ventricles. In addition, there was a large area adjacent to this where the right auricle had undergone hemorrhagic infarction. Pericarditis was found over both auricle and ventricle; and this case had auricular fibrillation.

Pericarditis and Pericardial Effusion. While localized pericarditis in heart disease was observed by Morgagni and, associated with more specific lesions, by Bérard, its nature was not comprehended until the pathology of infarction was studied. Ziegler and von Leyden gave good descriptions. Sternberg's comprehensive review of "pericarditis epistenocardia" covers the field down to his time. Data available from this series are tabulated and compared with several groups from the literature, as seen in table 18. (See also table 15—part II.) The lesion was observed in 28 per cent of all cases collected, and in 32 per cent of this series.

Pericardial effusion as a complication of infarct is rare^{36, 25} and it is probable that the most important factor in its production is congestive failure. There were 44 cases in this series with an effusion larger than 50 c.c. (table 18). In 17 of these there was no fresh pericarditis, but in every case there was some degree of failure.

Hydrothorax. Pleural transudation appeared in many cases as a sequel to congestive failure. In 47 cases it was equal on both sides and in 48 greater on the right (average difference 750 c.c.). There were eight cases with larger effusions on the left (average difference 275 c.c.). No morphological constant was found in the hearts. Most, but not all, had preponderant left ventricular damage, and râles had been heard in practically all cases examined during formation of hydrothorax.

SUMMARY

1. Congestive failure and shock followed in more than half of the acute attacks. Enlarged liver and jaundice were observed in a small proportion of cases.
2. Peripheral embolism was found most frequently in the second, third and fourth weeks. Many incidents considered clinically to be embolic were found to depend on local vascular faults.
3. No specific prognostic gauge was found to be valid in an individual case.

TABLE XVIII

Lesions of Pericardium

Fresh fibrinous pericarditis.....	52
Old adhesions.....	32
Obliterating adhesions (not constricting).....	6
Old and fresh pericarditis.....	3
Fresh obliterating pericarditis.....	3
Purulent pericarditis.....	2
"Uremic" pericarditis.....	2
"Organizing" clot after rupture.....	1

Effusion

cu. cm.	
50-75.....	10
75-100.....	16
100-150.....	5
150-200.....	6
200-250.....	4
250-300.....	2
400.....	1

Autopsy Findings of Pericarditis

Author	Number of Cases	Pericarditis
Huchard.....	31	7
Wearn.....	19	4
Wolff and White.....	23	11
Parkinson and Bedford.....	83	11
Levine.....	46	24
Lisa and Ring.....	100	10
Appelbaum and Nicolson.....	150	50
This series		
Recent.....	189	58
Old.....	111	41*
	752	213*

* 3 cases had old and recent.

TABLE XIX

Hydrothorax

	per cent	Average c.c.	Range c.c.
Present in 163 of 300.....	54		
* Bilaterally equal.....	47	575	100-2000
* Right side alone.....	15	700	100-2200
* Right greater than left.....	33		
Right side.....		1250	200-2800
Left side.....		500	100-1600
* Left greater than right.....	8		
Right.....		275	0-1000
Left.....		550	100-1500

* Cases which may have been influenced by pulmonary infarct, pleural infection, or obliterative pleural adhesions were discarded.

4. Causes of death were investigated and the predisposing influence of syncopal attacks was noted in cases of sudden death. Seasonal variation of death was in part influenced by seasonal fluctuation in incidence of acute attacks.

5. The left coronary tree was seriously involved in 84 per cent of cases, the right in 21 per cent. Nine cases of "ectopic infarction" appeared.

6. Twenty per cent of the infarcts followed arterial narrowing without thrombosis.

7. In four cases no arterial damage was detected.

8. Eight cases of coronary anomalies were found, one with a small coronary aneurysm.

9. The heart was enlarged in 83 per cent of the cases. The largest hearts were found in hypertensives.

10. Ventricular mural thrombi were found in nearly half the cases; emboli were detected twice as frequently in instances of right ventricular thrombi as in cases of mural thrombosis of the left ventricle. Some thrombi were present three years after acute infarction. Embolism was most frequent when the thrombus was attached to the interventricular septum.

11. Ventricular aneurysm was found in 10 per cent of the cases and appeared as early as the seventeenth day after infarction.

12. There were three cases of extensive calcification of scars.

13. Spontaneous rupture of the ventricle occurred in 17 cases. One survived rupture eight days. In one case an aneurysm was ruptured by a needle.

14. Four cases of coronary embolism from friable valvular vegetations were found, and there was one probable case in addition.

15. There were two auricular infarcts.

16. Pericarditis was found in 32 per cent of the cases and an effusion of 50 c.c. or more, in 15 per cent.

17. Hydrothorax was frequent, and in many cases was greater on the right.

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BIBLIOGRAPHY

1. ALLBUTT, C.: Diseases of the arteries, including angina pectoris, 1915, London.
2. APPELBAUM, E., and NICOLSON, G. H. B.: Occlusive diseases of the coronary arteries, *Am. Heart Jr.*, 1935, x, 662.
3. BARNES, A. R., and BALL, R. G.: The incidence and situation of myocardial infarction in one thousand consecutive postmortem examinations, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 215.
4. BARTELS, E. C., and SMITH, H. L.: Gross cardiac hypertrophy in myocardial infarction, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 452.
5. BENSON, R. L., HUNTER, W. C., and MANLOVE, C. H.: Spontaneous rupture of the heart, *Am. Jr. Path.*, 1933, ix, 295.

6. BÉRARD, P. H.: Paris Thesis, No. 23, 1826.
7. BERESFORD, E. H., and EARL, C. J. C.: Spontaneous cardiac rupture: a review of 46 cases, *Quart. Jr. Med.*, 1930, xxiv, 55.
8. BLUMER, G.: Pericarditis episthenocardia, *Jr. Am. Med. Assoc.*, 1936, cvii, 178.
9. CLOWE, G. M., KELLERT, E., and GORHAM, L. W.: Rupture of the right auricle of the heart, *Am. Heart Jr.*, 1934, ix, 324.
10. CORVISART, J. N.: *Essai sur les maladies et les lésions organiques du coeur*, Paris, 1806 (Gates Translation, 1812).
11. DAVENPORT, A. B.: Spontaneous heart rupture: a statistical summary, *Am. Jr. Med. Sci.*, 1928, clxxvi, 62.
12. HARRISON, T. F.: *Failure of the circulation*, 1935, Williams and Wilkins Company, Baltimore.
13. HIRSCHBOECK, F. J.: Calcification of the myocardium following coronary occlusion, *Am. Heart Jr.*, 1934, x, 265.
14. HUCHARD, H.: *Traité clinique des maladies du coeur et de l'aorté*, 1899, Paris, Ed. 3.
15. KRUMBHAAR, E. B., and CROWELL, C.: Spontaneous rupture of the heart, *Am. Jr. Med. Sci.*, 1925, clxx, 828.
16. LEARY, T.: Coronary spasm as a possible factor in producing sudden death, *Am. Heart Jr.*, 1935, x, 338.
17. LEVINE, S. A., and BROWN, C. L.: Coronary thrombosis: its various clinical features, *Medicine*, 1929, viii, 245.
18. LEVY, R. L., and BRUENN, H. G.: Acute fatal coronary insufficiency, *Jr. Am. Med. Assoc.*, 1936, cvi, 1080.
19. LEWIS, T.: *Diseases of the heart*, 1933, Macmillan Company, New York.
20. VON LEYDEN, E.: Über die Sclerose der Coronar-Arterien und die davon abhängigen Krankheitszustände, *Ztschr. f. klın. Med.*, 1884, vii, 459.
21. LIBMAN, E.: Methods of physical examination with special reference to painful disease of the thorax and abdomen, *Interstate Postgraduate Med. Assoc. N. Am.*, Cleveland Proc., Oct. 1926, 60.
22. LISA, J. R., and RING, A.: Myocardial infarction or gross fibrosis: (analysis of one hundred autopsies), *Arch. Int. Med.*, 1932, l, 131.
23. LONGCOPE, W. T.: The effect of occlusion of the coronary arteries on the heart's action and its relationship to angina pectoris, *Ill. Med. Jr.*, 1922, xli, 186.
24. MACCALLUM, W. G., and TAYLOR, J. S.: The typical position of myocardial scars following coronary obstruction, *Bull. Johns Hopkins Hosp.*, 1931, xli, 256.
25. MASTER, A. M., and JAFFE, H. L.: Coronary artery thrombosis with pericardial effusion, *Jr. Am. Med. Assoc.*, 1935, civ, 1212.
26. MASTER, A. M., DACK, S., and JAFFE, H. L.: Coronary thrombosis: an investigation of heart failure and other factors in its course and prognosis, *Am. Heart Jr.*, 1937, xiii, 330.
27. MEDLAR, E. M., and MIDDLETON, W. S.: Aneurysm of the left ventricle, *Am. Heart Jr.*, 1927-8, iii, 346.
28. MORGAGNI, J. G.: *De Sedibus et Causis Morborum, Venitiis, II Epist. 24 et seq. 1761.* (Translated by Benjamin Alexander, London, 1769.)
29. PALMER, J. H.: The prognosis following recovery from coronary thrombosis with special reference to the influence of hypertension and cardiac enlargement, *Quart. Jr. Med.*, 1937, xxx, 49.
30. PALMER, J. H.: The size of the heart after coronary thrombosis, *Canad. Med. Assoc. Jr.*, 1937, xxxvi, 387.
31. PARDEE, H. E. B., et. al.: Discussion at American Heart Association Meeting, June 1934; *Am. Heart Jr.*, 1935, x, 406.
32. PARKINSON, J., and BEDFORD, D. E.: Cardiac infarction and coronary thrombosis, *Lancet*, 1928, i, 4.

33. SALZMANN, H. A.: Spontaneous rupture of the heart simulating surgical abdominal disease, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 347.
34. SAPHIR, O.: Coronary embolism, *Am. Heart Jr.*, 1933, viii, 312.
35. SAPHIR, O., PRIEST, W. S., HAMBURGER, W. W., and KATZ, L. N.: Coronary arteriosclerosis, coronary thrombosis, and the resulting myocardial changes, *Am. Heart Jr.*, 1935, x, 567; 1935, x, 762.
36. SCHWARTZ, S. P.: Pericardial effusion following acute coronary vessel closure, *Am. Heart Jr.*, 1934, x, 253.
37. SHOOKHOFF, C., and DOUGLAS, A. H.: A case of acute coronary occlusion with roentgenographic evidence of the early development of an aneurysm of the left ventricle, *Am. Heart Jr.*, 1931, vii, 95.
38. STERNBERG, M.: Pericarditis epistenocardia, *Wien. med. Wchnschr.*, 1910, lx, 14.
39. WARNER, W. P., and DAUPHINEE, J. A.: Thrombosis of a coronary venous sinus in a case of thrombophlebitis migrans, *Am. Heart Jr.*, 1936, xii, 483.
40. WEARN, J. T.: Thrombosis of the coronary arteries with infarction of the heart, *Am. Jr. Med. Sci.*, 1923, clxv, 250.
41. WEIGERT, C.: *Virchow's Arch. f. path. Anat.*, 1880, lxxix, 106.
42. WEISS, S., and BAKER, J. P.: Carotid sinus reflex in health and disease, *Medicine*, 1933, xii, 297.
43. WEISS, S.: Syncope and related syndromes, *Oxford Med.*, 1935, ii, 250.
44. WHITTEN, M. B.: The relation of the distribution and structure of the coronary arteries to myocardial infarction, *Arch. Int. Med.*, 1930, xlv, 383.
45. WOLFF, L., and WHITE, P. D.: Acute coronary occlusion: report of twenty-three autopsied cases, *Boston Med. and Surg. Jr.*, 1926, cxcv, 13.
46. ZIEGLER, ERNST: Ueber Myomalacia Cordis, *Virchow's Arch. f. path. Anat.*, 1882, xc, 211.

THE PRESENT STATUS OF METHODS FOR THE PROPHYLAXIS OF ACUTE ANTERIOR POLIOMYELITIS *

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ACUTE anterior poliomyelitis is still among the important diseases in which knowledge of the mechanism of infection, its mode of dissemination and the factors responsible for epidemics, as well as the nature of natural and acquired immunity, is quite incomplete and controversial in many particulars and especially in relation to methods of prophylaxis.

Twenty-eight years ago Flexner and Lewis¹ first suggested that infection occurred through the upper respiratory tract and especially by way of the olfactory nerves. At least monkeys can be successfully inoculated by intranasal instillations of the virus and in spite of technical difficulties this virus has been found in the nasal and oropharyngeal washings of a small but sufficient number of human beings during and after attacks of the disease as well as in healthy individuals^{2, 3, 4, 5} to indicate that the upper respiratory tract is at least one avenue of infection; although the fact that epidemics commonly occur during July, August and September is not in conformity with what is observed in many other diseases transmitted by droplet or upper respiratory tract secretions for the highest incidence of such infections is more encountered during the colder months of the year. Furthermore, virus injected intracerebrally and intravenously in monkeys has been found in the oropharyngeal mucosa and washings suggesting that in human beings it may be excreted or eliminated as well as absorbed in these areas. More recent investigations by Schultz and Gebhardt,⁶ Lennette and Hudson,⁷ Gordon and Lennette,⁸ Sabin and Olitsky⁹ and others have definitely confirmed earlier observations that in monkeys the virus is absorbed by way of the olfactory tracts. The big and important question, however, and especially in relation to prophylaxis in human beings by nasal instillations of chemical agents for the blockage or destruction of virus, is whether the olfactory area is the *only* avenue of infection or whether this may include the upper respiratory tract in general. The latter possibility is suggested by the fact that the disease has been produced experimentally in monkeys by intratracheal inoculation with virus, as well as by the fact that the virus has been found in the tonsils and nasopharyngeal mucosa^{4, 10} of both human beings and monkeys.

Much stress has been laid upon the olfactory area as the portal of entry of the virus on the basis that section of the olfactory tracts prevents infection of monkeys inoculated intranasally and because Landon and Smith¹¹

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have found pathological changes in the tracts and bulbs of some human beings succumbing to the disease. Microscopical examination of 56 olfactory bulbs by these investigators, however, "has shown a surprisingly small amount of pathological change. There has frequently been edema and congestion, harbingers of more extensive damage, but in less than a fourth of them, do the characteristic cellular and infiltrative changes, as seen in the ganglia and nerve roots, appear. Either any inflammatory reaction in these organs is extremely short-lived, unlike the lesions of poliomyelitis elsewhere in the central nervous system, or the virus passes along these structures without leaving its identifying signature. A third possibility, which strikes us as more logical, in view of the essential difference in the nature of the pathological lesions, is that the olfactory bulb in human beings is not necessarily as frequent a pathway for the virus as is commonly held, and that nerve roots elsewhere are equally important portals of entry, possibly indirectly by way of the blood stream to their ganglia." Thus do these investigators with commendable conservatism conclude from their studies that the pathways of distribution of the virus do not seem to be as simply explained in human beings as in monkeys since they are inclined to the belief "that only direct extension by way of the nasopharynx and other nerve roots, but also the gastrointestinal tract and blood stream must be considered as very significant factors." In this connection it may be stated that Harmon and his colleagues¹² have failed to find histological changes of infection in the olfactory bulbs of nine cases of the 1936 Chicago epidemic. Under the circumstances I believe that in the present state of our knowledge we must suspect the possibility that infection with the virus takes place from the nasopharyngeal mucosa and even from the trachea in general as well as through the olfactory area and must agree that definite and recognizable tissue changes may not be produced by the virus in the avenues of infection.

If this is true the application of chemical agents to the olfactory area alone for the destruction of virus or the blockage of its absorption could not be expected to prove completely effectual as a prophylactic measure in human beings.

Unquestionably Sabin, Olitsky and Cox,¹³ Armstrong and Harrison,¹⁴ Schultz and Gebhardt^{15, 16} and others have effectually prevented infection of monkeys inoculated intranasally with virus by treatment of the olfactory area with picric acid and alum and particularly with zinc sulphate, but the picric acid-alum spray failed as a practical prophylactic measure in the Alabama epidemic of 1936 and the same may be stated in the case of the zinc sulphate mixture in the Toronto epidemic of 1937.¹⁷ It is true, however, that nasal spraying with picric acid and alum soon got out of control in Alabama so that a fair trial was impossible although even under these circumstances Armstrong¹⁸ thought that the actual incidence of poliomyelitis in the sprayed groups (25 cases) was somewhat less than the calculated incidence based on the attack rate in the unsprayed control group of the Birmingham area. Furthermore, in the Toronto epidemic, Tisdall and his

colleagues,^{19, 20} while employing the method of Peet, Echols and Richter,²¹ found it impractical to give treatment on three successive days but succeeded in giving two applications approximately 12 days apart. Of 4713 children treated in this manner with 0.5 to 1 c.c. of the mixture of 1 per cent zinc sulfate, 1 per cent pontocaine and 0.5 per cent sodium chloride solution, 11 developed poliomyelitis while 18 cases developed in an untreated control group of 6300. This difference in the attack rate is not statistically significant and while anosmia occurred in but 25 per cent as evidence of complete and effectual treatment of the olfactory area, yet the Toronto group of 44 otolaryngologists conducted the field investigation with such thoroughness and skill that in my opinion the results are a good and acceptable indication of what is to be expected from the solution and method of treatment employed. It is to be regretted, however, that three daily applications could not be employed as has been found effectual in monkeys but headache and other temporary disturbances made this impossible as a practical procedure. Whether or not treatment of the total olfactory area of human beings as indicated by complete anosmia will prove more effectual as a prophylactic measure remains to be determined and I think final judgment of the value of prophylaxis by applications of zinc sulfate to the olfactory area should await its trial under such conditions. But I doubt if an additional field trial of treatment with the DeVilbiss atomizer inserted between the nasal septum and middle turbinate will give any better results than observed by the Toronto group. For this reason a trial of the method proposed by Pentecost,²² consisting of the injection of 0.5 c.c. of the solution by means of a flexible olive tipped catheter with the head well down in the Proetz position, appears advisable since he reports that complete anosmia is obtained persisting for five days or longer without danger of possible injury to the mucosa or cribriform plate and with little likelihood of the solution entering the sphenoidal sinus or being swallowed. Nevertheless headache was noted in every case persisting for 2 to 6 hours and especially severe in individuals over 12 years of age, and there was stuffiness of the nose for 6 to 12 hours.

It is practically certain therefore that spraying of the nose with atomizers by the laity has failed and that the method of Peet and his colleagues cannot be successfully used on a broad scale since complete treatment of the olfactory area is difficult to obtain. Furthermore, it is not without hazard in unskilled hands. The catheter method employing the solution of zinc sulfate may prove more effectual although frontal headache may be severe and the anosmia may persist for months, especially in adults, suggesting either destruction of the olfactory endings, persistent edema or some other change as yet undetermined.²³ Nevertheless one or more applications of 1 per cent zinc sulfate solution may be worthy of trial during the next epidemic but the method is certainly of no value in the prophylaxis of sporadic cases and offers little or no hope of ultimately eliminating the disease.

Furthermore, I am personally prepared for disappointing results if it is true that virus may be absorbed from areas of the upper respiratory tract other than the olfactory area. Whether or not infection may occur through the skin and gastrointestinal tract is even more uncertain but both the possibility and probability are to be admitted. So far we have not been able to infect *Macacus rhesus* monkeys by feeding large doses of the M. V. strain of virus or by instilling by stomach tube as much as 10 to 20 c.c. of a 10 per cent suspension of monkey poliomyelitic spinal cord. It may be that *Macacus cynomolgus* is more susceptible to infection by this route²⁴ but the literature is quite controversial and indefinite.²⁵ Certainly it appears that the virus may escape destruction in the stomach and intestines of both monkeys and human beings since it has been found in the feces by several investigators²⁶ and more recently by Harmon¹² and Kramer,²⁷ but whether it represents merely swallowed virus or whether its presence indicates a gastrointestinal avenue of infection cannot be definitely stated at the present time. Toomey,^{28, 29} who has properly called attention to the late summer and autumnal prevalence of the disease as suggestive of its gastrointestinal origin and who has succeeded in producing it experimentally in monkeys by special methods of inoculation, believes that the toxins of enteric organisms and certain vitamin deficiencies may facilitate infection by this route but Hudson, Lennette and Gordon^{30, 31} have failed to infect monkeys by placing large amounts of virus in isolated loops of intestine. Under the circumstances it is commonly thought that the normal gastrointestinal tract of the monkey offers a barrier to infection^{32, 33} but that extraordinary measures, such as clamping the gut until the pinch reflex disappears and injecting the virus subserosally, may result in infection since under these circumstances virus may be absorbed by unmyelinated nerve fibers as it may in other parts of the body.

In other words, the general results of experimental investigations with monkeys strongly suggest that the virus is transported to the central nervous system by way of the axons of nerves from the portal of infection. It is certainly to be admitted moreover that most strains of the virus possess a striking selective affinity for these tissues and especially for those anterior horn cells of the spinal cord in which tetanus toxin also, regardless of the site of initial infection, tends to localize selectively. However, the possibility that the virus is absorbed through the mucosa of the upper respiratory tract into the lymphatics and blood with secondary localization in the central nervous system in a manner analogous to the pathogenesis of meningococcus meningitis is not to be lightly dismissed. It is true that the virus has not been detected so far in the blood of human cases of poliomyelitis but several investigators have found it in the blood of infected monkeys³⁴ and it is to be admitted that such technical difficulties are involved that small amounts of virus in the blood of human beings may escape detection. Burrows³⁵ has marshalled considerable data indicating that poliomyelitis may be essentially

and primarily an infection of the reticulo-endothelium of the body and Landon and Smith³⁶ on the basis of their thorough pathological studies in the 1931 epidemic in New York City state that, "whether the virus gains access to the central nervous system entirely by direct extension along the nerves of the nasopharynx, or entirely by way of the blood stream or both, we are inclined to believe that the systemic involvement of the reticulo-endothelial tissues plays an important part in the distribution of the lesions." Furthermore, if it is true that microglia and histiocytes are morphologically and functionally identical as stated by Dunning and Furth³⁷ it may be that the selective affinity of poliomyelitis virus for the tissues of the central nervous system is only an expression of its affinity for the reticulo-endothelium of the body in general and support the hypothesis that the disease is primarily an infection of this system.

In other words it appears on the basis of animal experiments that the upper respiratory tract is at least one important avenue of infection with absorption of virus by way of the olfactory nerves to the central nervous system but I do not think there is sufficient evidence for the assumption that the olfactory area is the sole pathway of infection. It appears both possible and probable that the virus may be absorbed from other areas of the respiratory tract and from any other portal initially infected and be transmitted by way of the axons of nerves or by way of the lymphatics and blood with consequent infection of the reticulo-endothelial tissues and central nervous system. For these reasons I have long thought that the greatest hope of successful prophylaxis of the disease lay in vaccination or active immunization.

That monkeys can be successfully vaccinated against acute anterior poliomyelitis has been amply proved by many investigators and especially with vaccines prepared of monkey poliomyelitic spinal cords carrying living or active virus. Unfortunately vaccines containing heat or chemically killed virus have not proved as effective as those incorporating at least some living virus. Brodie and Park³⁸ have found in both monkeys and children that virus treated with formalin for the minimum amount of time for rendering it non infective possessed some immunizing value. In my laboratory vaccines prepared of 4 per cent suspensions of monkey spinal cord carrying the M. V. strain of virus treated with 1 per cent sodium ricinoleate and administered by subcutaneous and intracutaneous injection have successfully immunized monkeys against both intracerebral and intranasal inoculation with virus.^{40, 41, 42} Of a total of 183 animals, 3 or 1.1 per cent developed paralysis during the period of immunization. All of these three occurred among the 124 animals given subcutaneous injections of the vaccine while none of 59 animals given intracutaneous injections developed any evidences of infection during immunization. It was my hope that this strain of virus had lost infectivity for human beings by reason of its long adaptation to the monkey, and especially after treatment with sodium

ricinoleate and when given by subcutaneous injection,⁴³ but the occurrence of nine cases of poliomyelitis among 10,725 individuals given the vaccine in 1935⁴⁴ has indicated that the virus apparently possesses infectivity for human beings and that this vaccine as well as the formalized vaccine of Park and Brodie is too dangerous for use.⁴⁵

I am convinced, however, that there is little or no hope of safe and effective vaccination against the disease unless active virus is employed. But the fact that considerable evidence has now accumulated to show that immunologically specific strains of virus may exist^{46, 47, 48, 49, 50} and that some of these may be highly infective by subcutaneous injection complicates the problem although it may be ultimately solved by vaccines made from cultures of living virus of non-neurotropic strains. The fact that one attack of the disease appears to leave a lasting immunity in the great majority of instances,^{51, 52} although second attacks may not be as rare as hitherto surmized,⁵³ and that the low attack rate among adults may be due to acquired immunity from a wide distribution of the virus with latent or clinically undetectable attacks of the disease with the development of antiviral antibody in the blood and placental extracts, still leaves one with considerable hope that vaccination may ultimately solve the problem of prophylaxis.

That vaccines and especially those containing living virus are capable of engendering the production of antiviral antibody is generally admitted but the ability of the antibody to prevent infection of the central nervous system has been questioned.^{54, 55} Over 90 per cent of monkeys immunized with vaccines of living virus by various investigators have shown the presence of this antibody in the blood on the basis of serum neutralization tests⁵⁶ and in my laboratory the majority immunized with ricinoleated vaccine were found completely protected against the intracerebral injection of virulent virus. Therefore, while I believe that the natural and acquired immunity of the disease is largely of the cellular or tissue type, yet it appears to be due in part at least to humoral resistance which may be ascribed to the presence of antiviral antibody in the blood.

Whether or not the antiviral antibody to be found in the blood of normal persons and of convalescents and in placental extracts possesses prophylactic value in human beings cannot be definitely stated. So far there has not been a sufficiently extensive and properly controlled study of it in this connection. Indeed this seems to be impossible insofar as convalescent serum is concerned. Under the circumstances I think we can and should base an opinion on the results of the use of such sera and extracts in the prophylaxis of the disease in monkeys inoculated both intracerebrally and intranasally with infective amounts of virus. On the basis of such evidence I believe that normal and convalescent sera containing large amounts of antibody have undoubtedly demonstrated their prophylactic activity when given in sufficiently large doses.⁵⁶ When the virus has actually attacked the cells of the central nervous system it appears to be beyond neutralization by antibody

as is under like circumstances the toxin of *Clostridium tetani* by tetanus antitoxin. I believe, however, that the virus of poliomyelitis may be effectually neutralized by antiviral antibody before such cellular invasion has occurred, although failures^{57, 58} are to be expected in this as in passive immunization against other acute infections with their respective immune sera. It is true that the therapeutic value of normal and convalescent serum has not been reflected in statistical studies but I am among the large number of physicians who believe that they have seen many individual cases where the early administration of serum and particularly blood transfusion may have effectually prevented progressive infection of the spinal cord. Not without interest in this connection is a recent report of Jackson¹⁷ on the use of serum in the 1936 epidemic in Manitoba stating that the injection of 20 c.c. in 395 cases within 36 hours to 4 days before the onset of paralysis resulted in the recovery of 86.1 per cent without residual paralysis and a mortality rate of 4.6 per cent as contrasted with 36.1 per cent residual paralysis and a mortality of 11.8 per cent among a group of 119 cases to whom serum was not given at all or after the onset of paralysis.

I believe therefore that the intramuscular injection of 20 to 40 c.c. of normal or convalescent serum known to contain antibody on the basis of monkey serum neutralization tests is still a hopeful prophylactic measure in children. The duration of the passive immunity is unknown but by analogy with other diseases probably does not last for over four weeks so that during epidemics two or more injections are required for sufficiently prolonging the degree of protection.

In conclusion brief reference may be made to the urgent need of a practical and clinically applicable test for susceptibility to poliomyelitis in view of its low attack rate. If such were available it would facilitate and greatly encourage efforts toward its prophylaxis not only with vaccines and sera but by the local treatment of the olfactory area with chemical agents as well. The problem is one of such importance as to richly merit the attention and efforts of investigators of this disease. Unfortunately the monkey serum neutralization test is at best only a rough measure of humoral immunity with no bearing at all upon the far more important phase of cellular or tissue resistance. It is, moreover, too expensive and time consuming for any possible practical application.⁵⁹ Various skin tests^{60, 61, 62} as well as complement fixation, precipitin and other reactions⁶³ have proved without value. We believe, nevertheless, that the problem may not be beyond ultimate solution.

SUMMARY

1. The results of experimental studies in poliomyelitis of monkeys show that the virus is absorbed by way of the olfactory nerves and microscopical examination of the olfactory bulbs in human cases of the disease also suggests that this is at least one avenue of infection in human beings.

2. Chemo-prophylaxis in human beings by the application of mixtures of picric acid and alum or of zinc sulfate to the olfactory area has failed but this may have been due to incomplete application of these agents.

3. Under present conditions the further trial of solutions of zinc sulfate is recommended by a method insuring more adequate treatment of the olfactory area.

4. It is possible, however, that the virus of poliomyelitis may be absorbed from the oropharyngeal mucosa, tonsils, trachea and even the intestinal tract and if this occurs in human beings treatment of the olfactory area alone cannot be expected to prove effective in the prophylaxis of the disease.

5. Monkeys have been successfully immunized against poliomyelitis with vaccines of the virus and especially those containing active virus but these are considered too dangerous for the vaccination of human beings.

6. Antiviral antibody contained in normal and convalescent human sera and placental extracts is capable of protecting monkeys against experimental poliomyelitis when administered in sufficiently large amounts. On this basis it appears quite probable that the antibody possesses some prophylactic value in human beings if administered before the virus has attacked the central nervous system.

7. In view of the low attack rate of poliomyelitis a practical test for susceptibility is urgently required since such would greatly facilitate the selective use of chemo-prophylaxis as well as prophylaxis by active and passive immunization. At the present time, however, such a test has not been discovered. The monkey serum neutralization test is not acceptable in this connection not only because of its expense and the time required to carry it out but likewise because it is not a measure of the more important cellular or tissue resistance of the disease.

BIBLIOGRAPHY

1. FLEXNER, S., and LEWIS, P. A.: Epidemic poliomyelitis in monkeys, *Jr. Am. Med. Assoc.*, 1910, liv, 45.
2. PAUL, J. R., and TRASK, J. D.: The detection of poliomyelitis virus in so-called abortive types of the disease, *Jr. Exper. Med.*, 1932, lvi, 319.
3. PAUL, J. R., TRASK, J. D., and WEBSTER, L. T.: Isolation of poliomyelitis virus from the nasopharynx, *Jr. Exper. Med.*, 1935, lxii, 245.
4. KRAMER, S. D.: Detection of a healthy carrier of virus of poliomyelitis without history of contact, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxii, 1165.
5. KRAMER, S. D., SOBEL, A. E., GROSSMAN, L. H., and HOSKWITH, B.: Survival of the virus of poliomyelitis in the oral and nasal secretion of convalescents, *Jr. Exper. Med.*, 1936, lxiv, 173.
6. SCHULTZ, E. W., and GEBHARDT, L. P.: Olfactory tract and poliomyelitis, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 728.
7. LENNETTE, E. H., and HUDSON, N. P.: Relation of olfactory tracts to intravenous route of infection in experimental poliomyelitis, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxii, 1444.
8. GORDON, F. B., and LENNETTE, E. H.: The blood stream in experimental poliomyelitis, *Jr. Bacteriol.*, 1938, xxxv, 43.

9. SABIN, A. B., and OLITSKY, P. K.: Fate of nasally instilled poliomyelitis virus in normal and convalescent monkeys, *Jr. Bacteriol.*, 1938, xxxv, 44.
10. FAIRBROTHER, R. W., and HURST, E. W.: The pathogenesis of, and propagation of the virus in, experimental poliomyelitis, *Jr. Path. and Bact.*, 1930, xxxiii, 17.
11. LONDON, J. F., and SMITH, L. W.: Poliomyelitis. Based on a study of the 1931 epidemic in New York City, 1934, MacMillan Company, New York, p. 50.
12. HARMON, P. H.: The use of chemicals as nasal sprays in the prophylaxis of poliomyelitis in man, *Jr. Am. Med. Assoc.*, 1937, cix, 1061.
13. SABIN, A. B., OLITSKY, P. K., and COX, H. R.: Protective action of certain chemicals against infection of monkeys with nasally instilled poliomyelitis virus, *Jr. Exper. Med.*, 1936, lxxiii, 877.
14. ARMSTRONG, C., and HARRISON, W. T.: Prevention of experimental intranasal infection with certain neurotropic viruses by means of chemicals instilled into the nostrils, *Pub. Health Rep.*, 1936, li, 203.
15. SCHULTZ, E. W., and GEBHARDT, L. P.: Prevention of intranasally inoculated poliomyelitis in monkeys by previous intranasal irrigation with chemical agents, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 133.
16. SCHULTZ, E. W., and GEBHARDT, L. P.: Zinc sulfate prophylaxis in poliomyelitis, *Jr. Am. Med. Assoc.*, 1937, cviii, 2182.
17. JACKSON, F. W.: The 1936 epidemic of poliomyelitis in Manitoba: control measures, *Canada Health Jr.*, 1937, xxviii, 363.
18. ARMSTRONG, C.: Experience with picric acid-alum spray in the prevention of poliomyelitis in Alabama, 1936, *Am. Jr. Pub. Health*, 1937, xxvii, 103.
19. TISDALL, F. F., BROWN, A., DEFRIES, R. D., ROSS, M. A., and SELLERS, A. H.: Zinc-sulphate nasal spray in the prophylaxis of poliomyelitis, *Canada Pub. Health Jr.*, 1937, xxviii, 523.
20. TISDALL, F. F.: Nasal spraying as a preventive of poliomyelitis, *Canada Pub. Health Jr.*, 1937, xxviii, 431.
21. PEET, M. M., ECHOLS, D. H., and RICHTER, H. J.: The chemical prophylaxis for poliomyelitis. The technic of applying zinc sulfate intranasally, *Jr. Am. Med. Assoc.*, 1937, cviii, 2184.
22. PENTECOST, R. S.: Zinc sulphate as a chemo-prophylactic agent in epidemic poliomyelitis, *Canada Pub. Health Jr.*, 1937, xxviii, 493.
23. SABIN, A. B., and OLITSKY, P. K.: Mode of action of zinc sulfate spray in preventing infection with nasally instilled poliomyelitis virus, *Jr. Bacteriol.*, 1938, xxxv, 44.
24. LEVADITI, C., KLING, C., and LÉPINE, P.: Nouvelle recherches expérimentales sur la transmission de la poliomyélite par la voie digestive. Action du chlore sur le virus poliomyélique, *Bull. Acad. de méd.*, 1931, cv, 190.
25. International Committee for the Study of Infantile Paralysis, 1931, Williams and Wilkins Company, Baltimore, p. 85 and 257.
26. See reference 25, page 78.
27. KRAMER, S. D.: Personal Communication.
28. TOOMEY, J. A.: Active and passive immunity and portal of entry in poliomyelitis, *Jr. Am. Med. Assoc.*, 1937, cix, 402.
29. TOOMEY, J. A.: Ingestion of vitamins A, B, C and D and poliomyelitis, *Am. Jr. Dis. Child.*, 1937, liii, 1202.
30. HUDSON, N. P., LENNETTE, E. H., and GORDON, F. B.: Factors of resistance in experimental poliomyelitis with comments on immunity in poliomyelitis, *Jr. Am. Med. Assoc.*, 1936, cvi, 2037.
31. LENNETTE, E. H., and HUDSON, N. P.: Failure to infect monkeys with poliomyelitis virus through isolated intestinal loops, *Jr. Infect. Dis.*, 1936, lviii, 10.
32. FABER, H. K.: Acute poliomyelitis as a primary disease of the central nervous system, *Medicine*, 1933, xii, 83.

33. FLEXNER, S.: Respiratory versus gastro-intestinal infection in poliomyelitis, *Jr. Exper. Med.*, 1936, lxiii, 209.
34. International Committee for the Study of Infantile Paralysis, 1931, Williams and Wilkins Company, Baltimore, p. 73.
35. BURROWS, M. T.: Is poliomyelitis a disease of the lymphatic system? *Arch. Int. Med.*, 1931, xlviii, 33.
36. LANDON, J. F., and SMITH, L. W.: Poliomyelitis. Based on a study of the 1931 epidemic in New York City, 1934, MacMillan Company, New York, p. 39.
37. DUNNING, H. S., and FURTH, J.: Studies on the relation between microglia, histiocytes and monocytes, *Am. Jr. Path.*, 1935, xi, 895.
38. BRODIE, M., and PARK, W. H.: Active immunization against poliomyelitis, *Trans. Fourth Annual Meeting, Southern Branch of Am. Publ. Health Assoc.*, 1935, p. 71.
39. KOLMER, J. A.: An improved method of preparing the Kolmer poliomyelitis vaccine, *Am. Jr. Publ. Health*, 1936, xxvi, 149.
40. KOLMER, J. A., and RULE, A. M.: A successful method for vaccination against acute anterior poliomyelitis: preliminary report, *Am. Jr. Med. Sci.*, 1934, clxxxviii, 510.
41. KOLMER, J. A., KLUGH, G. F., and RULE, A. M.: A successful method for vaccination against acute anterior poliomyelitis: further report, *Jr. Am. Med. Assoc.*, 1935, civ, 456.
42. KOLMER, J. A., and RULE, A. M.: Active immunization against acute anterior poliomyelitis with ricinoleated vaccine, *Jr. Immunol.*, 1937 xxxii, 341.
43. KOLMER, J. A.: Susceptibility and immunity in relation to vaccination in acute anterior poliomyelitis, *Jr. Am. Med. Assoc.*, 1935, cv, 1956.
44. KOLMER, J. A.: Vaccination against acute anterior poliomyelitis, *Am. Jr. Pub. Health*, 1936, xxvi, 126.
45. LEAKE, J. P.: Poliomyelitis following vaccination against the disease, *Jr. Am. Med. Assoc.*, 1935, cv, 2152.
46. BURNET, F. M., and MACNAMARA, J.: Immunological differences between strains of poliomyelitis virus, *Brit. Jr. Exper. Path.*, 1931, xii, 57.
47. WEYER, E. R.: Immunological differences between a strain of monkey virus and human poliomyelitis virus, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxix, 289.
48. PAUL, J. R., and TRASK, J. D.: Strains of poliomyelitis virus, *Jr. Exper. Med.*, 1937, lviii, 513.
49. TRASK, J. D., PAUL, J. R., BEEBE, A. R., and GERMAN, W. J.: Viruses of poliomyelitis; immunologic comparisons of six strains, *Jr. Exper. Med.*, 1937, lxxv, 687.
50. KESSEL, J. F., STIMPERT, F. D., and FISK, R. T.: Studies with poliomyelitis virus. II. Immunologic comparison of a Los Angeles strain of virus with the M. V. strain, *Jr. Bacteriol.*, 1938, xxxv, 42.
51. STILL, G. F.: Second attacks of acute poliomyelitis and the minimal duration of immunity, *Arch. Dis. Child.*, 1930, v, 295.
52. QUIGLEY, T. B.: Second attacks of poliomyelitis. Review of the literature and report of a case, *Jr. Am. Med. Assoc.*, 1934, cii, 752.
53. FISCHER, A. E., and STILLERMAN, M.: Does an attack of acute anterior poliomyelitis confer adequate immunity? *Jr. Am. Med. Assoc.*, 1938, cx, 569.
54. SCHULTZ, E. W., and GEBHARDT, L. P.: Observations on the prophylactic value of specific immune serum in experimental poliomyelitis, *Jr. Pediat.*, 1935, vii, 332.
55. OLITSKY, P. K., and COX, H. R.: Experiments on active immunization against experimental poliomyelitis, *Jr. Exper. Med.*, 1936, lxiii, 109.
56. KOLMER, J. A.: Antibody in relation to immunity in acute anterior poliomyelitis, *Jr. Immunol.*, 1936, xxxi, 119.
57. HARMON, P. H., and HARKINS, H. N.: The significance of neutralizing substances in resistance and recovery from poliomyelitis, *Jr. Am. Med. Assoc.*, 1936, cvii, 552.
58. HARMON, P. H., and HARKINS, H. N.: Occurrence of virucidal substances in patients

- with poliomyelitis: bearing on serum treatment and vaccination, *Illinois Med. Jr.*, 1936, September.
59. KOLMER, J. A., and RULE, A. M.: Tests for immunity to acute anterior poliomyelitis. The technic and status of the monkey serum neutralization or antiviral test, *Jr. Immunol.*, 1935, xxix, 175.
 60. HARMON, P. H., HARRISON, J. A., and KERNWEIN, G.: Skin tests for sensitivity to virus of poliomyelitis, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1134.
 61. SABIN, A. B., PARK, W. H., and JUNGBLUT, C. W.: Nature of skin reactions produced by heat inactivated poliomyelitis virus, *Arch. Int. Med.*, 1933, li, 878.
 62. KOLMER, J. A., KLUGH, G., and RULE, A. M.: Tests for immunity to acute anterior poliomyelitis: skin reactions to virus, *Jr. Immunol.*, 1935, xxix, 191.
 63. KOLMER, J. A., and RULE, A. M.: Tests for immunity to acute anterior poliomyelitis: colloidal gold, complement fixation and precipitation tests, *Jr. Immunol.*, 1935, xxix, 199.

A STUDY OF THE CHANGES IN SERUM CHOLESTEROL, GASTRIC SECRETION AND CARBOHYDRATE METABOLISM IN PATIENTS WITH TOXIC GOITER*

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IN 1922, Epstein and Lande¹ studied the blood cholesterol of 24 patients, 14 of whom had exophthalmic goiter and 10 of whom had toxic nodular goiter. The conclusion from this group was that, in general, the decrease in blood cholesterol bears a direct relationship to the extent of increase of the basal metabolic rate. In nine of the 14 cases this was true. The lowest basal metabolic rate of plus 14 corresponded to a blood cholesterol of 196 mg. per 100 c.c., and the highest basal rate of plus 82 to a cholesterol of 90 mg. However, in this group the relationship was not invariable. In the toxic nodular group of 10 the relationship of the basal metabolic rate and cholesterol was not nearly as definite. Gardner and Gainsborough² in 1928 studied the serum cholesterol in 14 toxic cases and found no evidence to support the belief of an inverse relationship between the cholesterol and basal metabolic rate in hyperthyroidism. Mason, Hunt, and Hurxthal³ found an average blood cholesterol value of 130 mg. per 100 c.c. in 47 patients with toxic goiter whose average basal metabolic rate was plus 57. Hurxthal⁴ reported average cholesterol values in patients with toxic nodular goiter below the normal range and still lower values in patients with exophthalmic goiter. The lowest values occurred in patients in or near thyroid crisis; the next lowest in patients with auricular fibrillation. Later Hurxthal⁵ found that after surgical treatment the blood cholesterol increased as much in patients with exophthalmic goiter as in those with toxic adenomatous goiter.

We determined the serum cholesterol of 50 patients with hyperthyroidism, 18 of whom had exophthalmic goiter with an average basal metabolic rate of plus 56, and 32 of whom had toxic nodular goiter with an average basal metabolic rate of plus 35. The serum cholesterol determination was done by the method of Forbes and Irving.⁶ The majority of the patients had received some iodine prior to admission. In the exophthalmic group the cholesterol values ranged from 200 to 67 mg. per 100 c.c., the high cholesterol value corresponding to a basal metabolic rate of plus 21 and the low to a basal metabolic rate of plus 80. The average cholesterol for this group was 136 mg. per 100 c.c. (chart 1). In a recheck of these same 18 patients in a period varying from 4 to 18 months after operation we

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found the average blood cholesterol to be 190 mg. per 100 c.c. with an average basal metabolic rate of plus 11. There was an increase in blood cholesterol value in all except two patients. These two were only mildly toxic before operation and were free of symptoms when rechecked. In three patients, on whom thyroidectomy was done in stages, some interesting changes were seen in these values. In the case of a 17 year old girl, a cholesterol of 108 mg. per 100 c.c. occurred with a basal metabolic rate of plus 55. A hemithyroidectomy was done and four months later the cholesterol value was 145 mg. per 100 c.c. with a basal metabolic rate of a plus 12. At this time the other side was operated upon. A check on this patient four months after the last operation showed a cholesterol value of 175 mg. per 100 c.c. with a basal metabolic rate of a minus 22. Another, a male 24

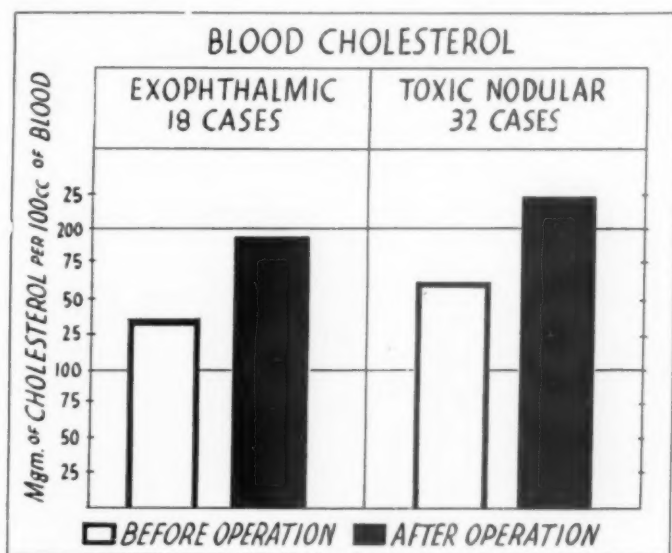


CHART 1.

years of age, had a cholesterol value of 90 mg. per 100 c.c. with a basal metabolic rate of plus 85. Two months after a hemithyroidectomy the cholesterol value was 67 mg. per 100 c.c. with a basal metabolic rate of plus 80. The cholesterol value four months after the second operation was 132 mg. per 100 c.c. with a basal metabolic rate of minus 17. The third, a male aged 50, had a cholesterol of 132 mg. per 100 c.c. with a basal metabolic rate of plus 53. A hemithyroidectomy was done and a study six months later showed a cholesterol value of 115 mg. per 100 c.c. with a basal metabolic rate of plus 77. A study six months after the second operation showed a cholesterol value of 202 mg. per 100 c.c. with a basal metabolic rate of plus 37. One patient, a female aged 45, was admitted in a severe thyroid crisis. Her cholesterol value at this time was 144 mg. per 100 c.c. with a

basal metabolic rate of plus 58. The patient refused operation and a study two months later showed a cholesterol value of 167 mg. per 100 c.c. with a basal metabolic rate of plus 42. At this time the patient had a sub-total thyroidectomy and a check 10 months from the time of operation showed a cholesterol value of 188 mg. per 100 c.c. with a basal metabolic rate of plus 10.

In the group of 32 patients with toxic nodular goiter the average cholesterol value before operation was 159 mg. per 100 c.c., and after operation the average was 224 mg. (chart 1). All cases except three showed a definite increase after operation. The cholesterol values of the three which did not show an increase were nearly the same as before operation.

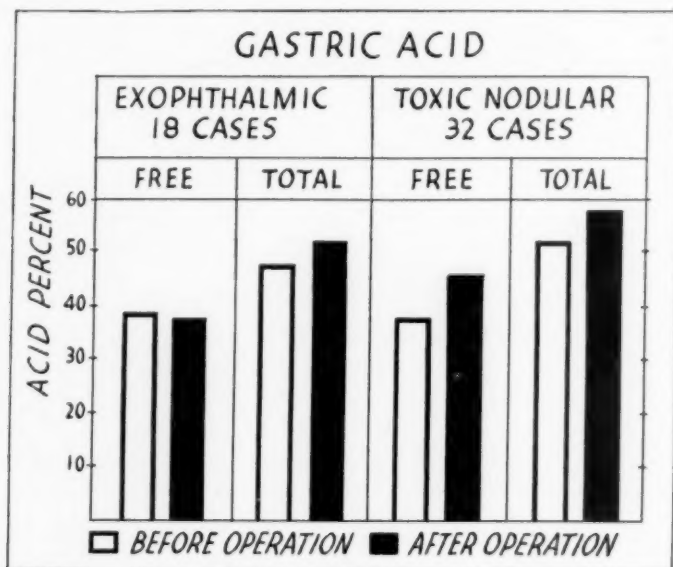


CHART 2.

The inverse relationship between the blood cholesterol and basal metabolic rate was not definite by any means in either of these groups; however, there was some tendency for this in the exophthalmic group. There was no tendency for an inverse relationship in the toxic nodular group (charts 3 and 4).

Several workers have reported a low gastric acidity and an increased incidence of anacidity in hyperthyroidism but the results were obtained by such test meals as Ewald and not by histamine stimulation. Lerman, Pierce, and Brogan⁷ using 50 c.c. of 7 per cent alcohol as a test meal and 0.5 mg. of histamine injected subcutaneously, determined the acid value in 200 normals, distributed fairly evenly between the ages of 20 and 69, as follows: free acid 40.4 c.c. of N/10 HCl for 100 c.c. and total acid approximately 10

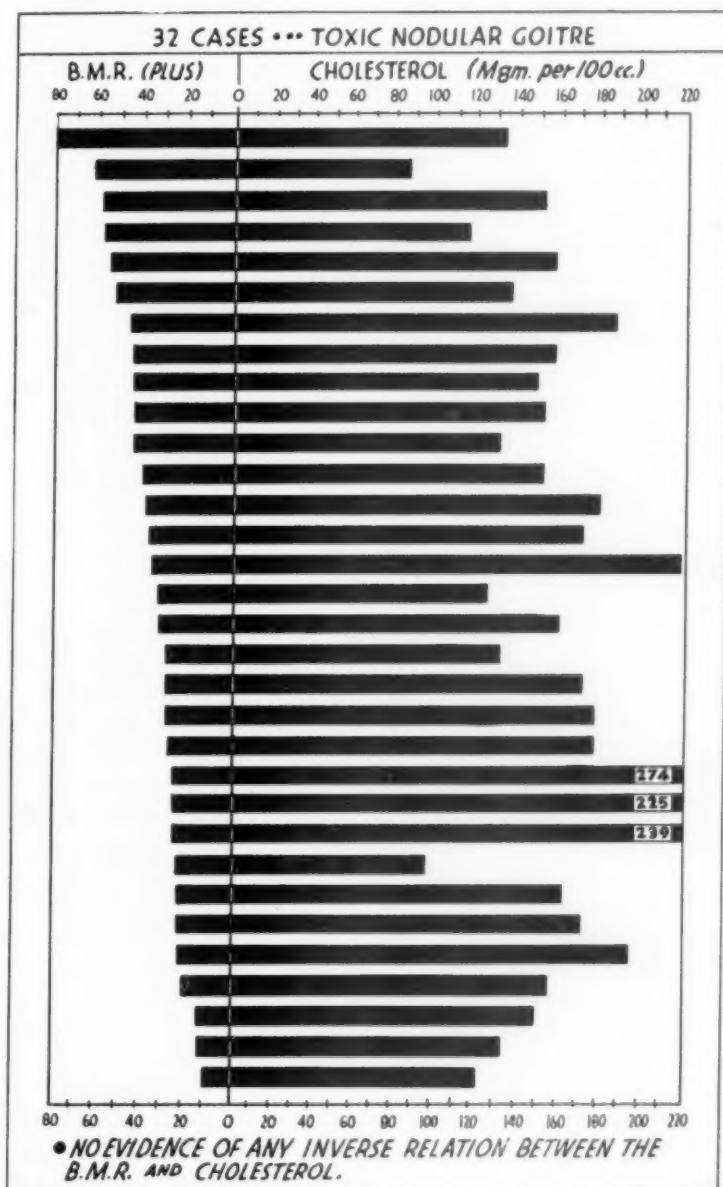


CHART 3.

points more. They reported an incidence of 13 per cent anacidity, 16.5 per cent hypoacidity, 49.5 per cent normal acidity, and 21 per cent hyperacidity. In 50 patients with exophthalmic goiter Lerman and Means⁸ found an anacidity of 38 per cent with a definite tendency to hypoacidity. Wilkin-son,⁹ using a test meal of 50 c.c. of 7 per cent alcohol and 0.1 mg. of histamine subcutaneously for each 10 kg. of weight, found the average free acid in patients with toxic goiter to be 24 c.c. and total acid 36.9 c.c. of N/10 HCl for 100 c.c. In this study there was an anacidity in 36 per cent. He

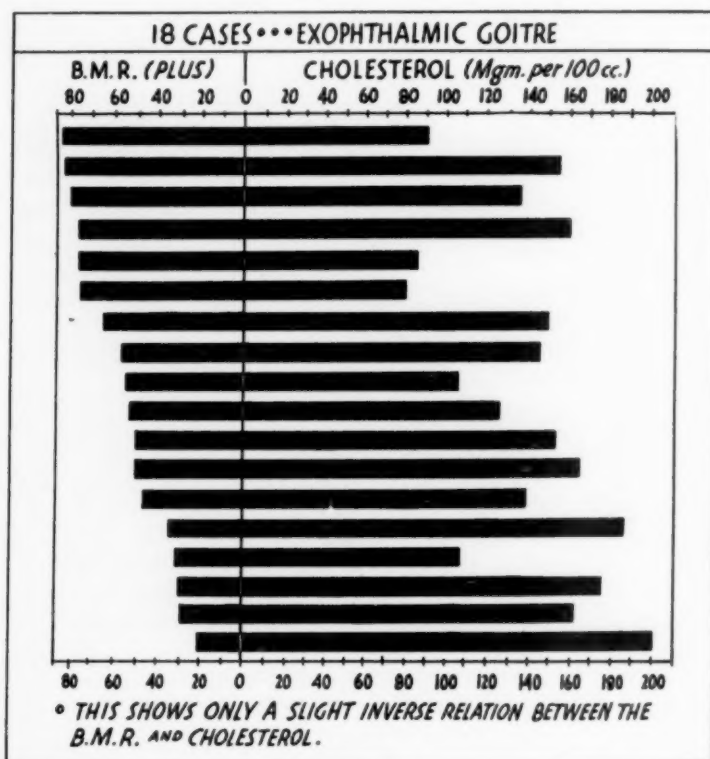


CHART 4.

studied 114 cases three months or longer after operation and found an anacidity of only 10.5 per cent. The average free acid after operation was 46 c.c. of N/10 HCl for 100 c.c. He was able to recheck 25 of the patients who showed achlorhydria before operation and found that 22 of the 25 had regained free acid. The average duration of symptoms before operation was 9.2 months in the entire group, whereas in the group that there was no free acid the average duration of symptoms was 16.6 months. He suggests that the development of achlorhydria depends on the duration rather than the degree of toxicity.

Our gastric analyses were done with the test meal of 200 c.c. of 7 per cent alcohol and subcutaneous injection of 0.5 mg. histamine in the male and 0.2 mg. in the female. The stomach contents were aspirated every 15 minutes for one hour. The unit used to express the acid is the maximal c.c. of N/10 HCl of 100 c.c. obtained in any one specimen. In the 18 patients with exophthalmic goiter the ages varied from 17 to 56 with a fairly even distribution. The average free acid before operation was 39.3 with a total of 47.2; the average free acid four to 18 months after operation was 38.2 with a total acid of 52.2 (chart 2). Four of these 18, or 22 per cent had no free acid; on the recheck three of the same showed no free acid while

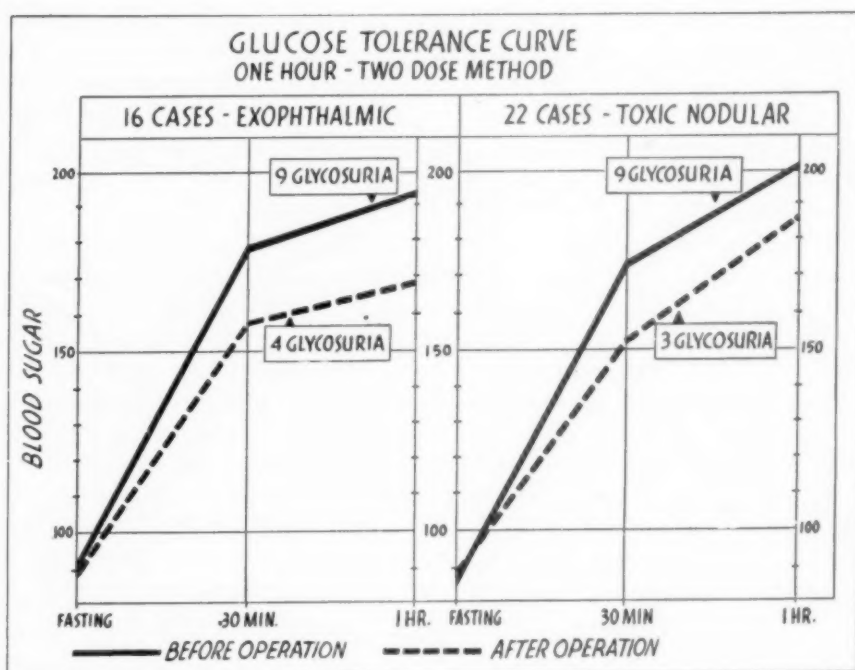


CHART 5.

one showed 20. The average length of duration of the toxic symptoms in this group was 30 months, whereas the average length of duration of the toxic symptoms of the four who had no free acid was 33 months. There was no definite relationship between the toxicity and the degree of acidity.

In the 32 patients with toxic nodular goiter the average free acid before operation was 37.3 with a total of 51.5. The recheck after operation showed an average free acid of 46.7 with a total of 58.5 (chart 2). Before operation there were two patients or 6.3 per cent who showed achlorhydria and the same two did not have any free acid when rechecked. However, there was one on the recheck that had an anacidity which had a free acid of

22 before a thyroidectomy. The age of these patients ranged from 24 years to 62 with a fairly even distribution in the various age groups. The average duration of toxic symptoms in this group was 25 months, whereas the duration was 24 and 36 months in the two patients with no free acid.

This series of 50 patients with toxic goiter showed six cases or 12 per cent anacidity before operation with exactly the same after operation. The incidence of achlorhydria in the exophthalmic group was somewhat above the figure given for normal but the occurrence of anacidity in the toxic nodular group was less than that given for normal.

In hyperthyroidism there is impairment in carbohydrate metabolism as determined by the glucose tolerance test and glycosuria. Geyelin¹⁰ studied the glucose tolerance in 27 cases of hyperthyroidism. When he compared the findings with normals he concluded that there is a slowed return to fasting blood sugar value after doses of glucose, and that this is more marked in proportion to the severity of the case. John¹¹ studied 82 patients with hyperthyroidism and 10 of colloid goiter. He found a decreased glucose tolerance curve in 66 per cent and glycosuria in 19 per cent. These were selected cases of hyperthyroidism and do not represent the average incidence of impaired carbohydrate metabolism. In this series there was no relationship between the degree of impairment and the severity of the disease. John¹² later reported his findings of the glucose tolerance curve on 239 cases of hyperthyroidism. These were also selected patients and showed within $1\frac{1}{2}$, the same percentage with glucose tolerance impairment, as the previous 82 cases. Gardner-Hill, Brett, and Smith¹³ studied the glucose tolerance in four patients with severe exophthalmic goiter and found a decreased tolerance and glycosuria in each instance. Wilder and Sansum¹⁴ studied the glucose tolerance of five patients with exophthalmic goiter and found it decreased in each case.

Our studies of carbohydrate metabolism were done by the one hour, two dose glucose tolerance test as described by Exton and Rose.¹⁵ The criteria that are given as normal are: A fasting blood sugar within the normal limits of the particular blood sugar method employed; a rise in the blood sugar which does not exceed 75 mg. in the 30 minute sample; the blood sugar in the 60 minute sample is less, the same, or does not exceed the 30 minute sample by more than 5 mg.; all urine samples are negative to Benedict's test. It seemed to us after several tests on normal individuals that these criteria are not met; so we have made no attempt to compare our curves with that given by Exton and Rose, but have compared the preoperative curve with that determined several months after operation. The patients who were diabetics were not included in this study. In the exophthalmic group of 18 we had a preoperative glucose tolerance study of 16, and a postoperative study in the same 16. Before operation the average glucose tolerance curve showed a fasting blood sugar of 92.5 mg. per 100 c.c., at the end of the one-half hour 179.3 mg., and at the end of the hour 192.8 mg. Nine or 56.2 per cent of these 16 showed glycosuria at the end of the hour. Several

months after operation the average fasting blood sugar was 90.8 mg., at the end of the one-half hour 157.8 mg., and at the end of the hour 168.9 mg. (chart 5). Four patients or 22 per cent showed glycosuria, three of which showed glycosuria before operation and one did not. There was no definite relationship between the degree of toxicity and the decrease in carbohydrate metabolism. The patient admitted in crisis showed a fasting blood sugar of 110 mg. per 100 c.c., 258 mg. at the end of the one-half hour, and 207 mg. at the end of the hour. Some sugar was found in the urine specimen at the end of the hour. Recheck several months after the crisis showed a fasting blood sugar of 92 mg. per 100 c.c., 194 mg. at the end of the one-half hour, and 260 mg. at the end of the hour. The urine specimen at the end of the hour contained sugar. Several months after this patient had a subtotal thyroidectomy her fasting blood sugar was 90 mg. per 100 c.c., 156 mg. at the one-half hour, and 126 mg. at the end of the hour. There was no glycosuria.

In the toxic nodular group we had preoperative and postoperative carbohydrate metabolism studies in 22 patients. The average curve before operation showed a fasting blood sugar of 85.9 mg. per 100 c.c., 173.5 mg. at the end of the one-half hour, and 201.1 mg. at the end of the hour. There were 9 or 40.9 per cent that had glycosuria at the end of the hour. After operation the average fasting blood sugar was 89.8 mg. per 100 c.c., at the end of the one-half hour 152.4 mg. and at the end of the hour 185.6 mg. (chart 5). There were three patients or 13.6 per cent who showed glycosuria, two of whom had glycosuria before operation and one did not.

SUMMARY AND CONCLUSIONS

1. While there is a general tendency for the cholesterol values to be low in patients suffering from hyperthyroidism, we could demonstrate no definite inverse relationship between the degree of toxicity as measured by the basal metabolic rate and serum cholesterol level. In patients with exophthalmic goiter there is only a slight tendency toward an inverse relationship between the degree of toxicity as measured by the basal metabolic rate and level of the serum cholesterol. In patients suffering with toxic nodular goiter this tendency was not evident. Generally speaking, the cholesterol values were definitely higher after operation, the degree of increase being essentially the same in the two groups.

2. Acid figures obtained in this study as to the frequency of anacidity do not agree with those of Lerman and Means and Wilkinson, although this is a smaller group. There was no relationship between the degree of toxicity and the amount of acid. The incidence of anacidity in this group before and after operation was 12 per cent. The average free acid in the exophthalmic patients was slightly less after operation, while in the 32 patients with toxic nodular goiter it was increased somewhat.

3. There was frequently an improvement in carbohydrate metabolism after operation as measured by the glucose tolerance curve and glycosuria.

BIBLIOGRAPHY

1. EPSTEIN, A. A., and LANDE, H.: Studies on blood lipoids; the relationship of cholesterol and protein deficiency to basal metabolism, *Arch. Int. Med.*, 1922, xxx, 563-577.
2. GARDNER, J. A., and GAINSBOROUGH, H.: The relationship of plasma cholesterol and basal metabolism, *Brit. Med. Jr.*, 1928, ii, 935-937.
3. MASON, R. L., HUNT, H. M., and HURXTHAL, L. M.: Blood cholesterol values in hyperthyroidism and hypothyroidism—their significance, *New England Jr. Med.*, 1930, cciii, 1273-1278.
4. HURXTHAL, L. M.: Blood cholesterol in thyroid disease; analysis of findings in toxic and non-toxic goitres before treatment, *Arch. Int. Med.*, 1932, li, 22-32.
5. HURXTHAL, L. M.: Blood cholesterol in thyroid disease; effect of treatment, *Arch. Int. Med.*, 1933, lii, 86-95.
6. FORBES, J. C., and IRVING: The determination of cholesterol in whole blood, *Jr. Lab. and Clin. Med.*, 1930, xvi, 909-912.
7. LERMAN, J., PIERCE, F. D., and BROGAN, A. J.: Gastric acidity in normal individuals, *Jr. Clin. Invest.*, 1932, xi, 155-165.
8. LERMAN, J., and MEANS, J. H.: Gastric secretion in exophthalmic goitre and myxedema, *Jr. Clin. Invest.*, 1932, xi, 167-182.
9. WILKINSON, S. A.: Gastric acidity in thyroid dysfunction, *Jr. Am. Med. Assoc.*, 1922, ci, 2,097-2,099.
10. GEYELIN, H. R.: The carbohydrate metabolism in hyperthyroidism as determined by examination of blood and urine, *Arch. Int. Med.*, 1915, xvi, 975-988.
11. JOHN, H. J.: Carbohydrate metabolism in hyperthyroidism, *Endocrinology*, 1917, xi, 497-578.
12. JOHN, H. J.: A study of 1,100 glucose tolerance tests, *Med. Jr. and Rec.*, 1930, cxxxi, 287.
13. GARDNER-HILL, B. H., BRETT, P. C., and SMITH, J. F.: Carbohydrate metabolism in myxedema, *Quart. Jr. Med.*, 1925, xviii, 327-334.
14. WILDER, R. M., and SANBURN, W. D.: Glucose tolerance in health and disease, *Arch. Int. Med.*, 1917, ix, 310-334.
15. EXTON, W. G., and ROSE, A. R.: The one hour two-dose dextrose tolerance test, *Am. Jr. Clin. Path.*, 1934, iv, 381-399.

TRENDS IN PUBLIC HEALTH*

By THOMAS PARRAN, M.D., F.A.C.P., *Washington, D. C.*

PUBLIC health is one of the newest and the most rapidly growing specialties of medicine. This has been due to a number of factors among which are:

1. The growth of scientific medical knowledge makes possible effective means of prevention and treatment for an increasing number of diseases.

2. The increasing concern of man for the well-being of his fellow man. This growth in the sentiment against suffering, as Newsholme calls it, has found expression in a large structure of social laws, the effort to provide more nearly adequate measures of relief for the destitute, unemployment insurance, and many other enactments.

3. The transition from an agrarian to an industrial economy has increased the interdependence of the population. An industrial civilization with workers dependent upon a daily wage leaves them more exposed to the risks of dependency. They are victimized by the play of economic forces beyond the power of the individual to control.

4. Good health is a factor in physical efficiency; therefore in national efficiency. Conversely, the ill health of individual citizens lowers the nation's fitness, lessens its chance of survival in a warring world, and depletes city, state and federal budgets.

If medicine were a static or a decadent science, public health—which means putting medicine to work for the whole people—would stand still or regress. On the contrary, medicine, as we all know, is perhaps the most dynamic of the sciences. Public health action, through which the beneficence of medicine is canalized for the common good, should keep abreast of medical advances.

Formerly the rich had good medical care as a privilege. During the last generation the poor in some cities have had it as a matter of charity. We now have reached a stage in the evolution of citizenship when all the people, poor and rich alike, are beginning to demand at least a minimum of health protection as a right. Our plans for distributing such health protection must be based on the concept of an equal opportunity to be born healthful, to maintain health, to prevent needless disease, unnecessary disablement, and premature death. To the informed modern mind, this opportunity for health is beginning to rank with the other basic equalities of American life—freedom of speech, of faith, of assembly, of franchise. No man can fully exercise his rights and privileges if he has not also the inalienable privilege of health. There is no citizen, however patriotic, but is embittered if he knows that to some are given the privileges of healthful living while to him they are denied.

* Read at the New York meeting of the American College of Physicians, April 4, 1938.

Those of us who practice the specialty of public health accept as our major function the application to mass health of life saving methods worked out with endless patience in the research laboratory, at the bedside, and in the field. It follows that each accretion to our present knowledge both of prevention and the cure of disease extends the scope of public health.

A corollary of the growth of medical knowledge is that it increases the cost of applying the sum total of that knowledge for the benefit of the patient. This means that good medical care is beyond the reach of an increasing number of persons, for the treatment of disease increasingly calls for coördination of many technics, facilities, and the collaborative wisdom of many specialists.

In an earlier day the problem was simple. The health officer did what he could to prevent disease, chiefly through sanitation and quarantine measures. On the other hand, the family doctor could carry in his head most of the medical knowledge of the day and in his little black bag most of the ways and means of using it. That day has passed. Yearly we are confronted with a larger list of diseases which can be prevented in the community as a whole if sick persons are treated promptly. I need not detail them to this audience. Even the layman knows that this is true of syphilis, of tuberculosis, to a certain extent of cancer and of other diseases which leave a tragic trail of disablement and death. Even the layman knows that a large proportion of infant and maternal deaths are unnecessary.

When medicine was an empirical art and not yet science, it mattered little whether or not the mass of the people had the services of the medicine man and the barber surgeon. Now, however, the community is beginning to concern itself with the prevention, alleviation and cure of all sickness, disability and premature death, just as it protects itself against burglaries, embezzlement, arson, and murder. Both disease and crime are economic waste. By taking the proper precautions, much of both can be prevented from doing serious damage to the community.

Public health services result from community interest in them. Such interest is spontaneous and continued when inspired by good health teaching to show the goal and by medical leadership which is genuinely concerned to work out a method of attaining that goal. Public health, then, embraces the prevention and cure of all diseases which because of their wide prevalence, their serious nature, or their costly treatment cannot be dealt with adequately by the individual efforts of the patient. In addition to the examples I have suggested—syphilis, tuberculosis, and cancer which, in the light of our present knowledge, can be controlled most readily through early treatment of the patient—this definition of prevalence, seriousness or cost may be illustrated further by the care of the insane, which is beyond the financial resources of the average family, the campaign against pneumonia, the after-care of poliomyelitis, the treatment of the disabling chronic diseases, and the provision of all medical care for the dependent groups of the population.

It is also a function of public health to pursue scientific research and investigations which have for their object better methods of preventing and treating those diseases against which our scientific weapons now are not effective.

The changes in the concept and scope of public health have complicated relationships between public and individual efforts to give medical care and to protect health. To my mind, most of the complications are needless. Unfortunately, we have not always maintained the same dispassionate point of view toward these relationships which has characterized our search for truth in the laboratory and at the bedside of the patient. Many of our finest physicians have given little or no attention to the broad problems of disease prevalence and the proved public health methods of dealing with certain diseases. It is equally true that many of our ablest public health administrators have lost touch with the personal problems and the clinical viewpoint of the private practitioner. In viewing the whole status of medicine and public health today, we need to know enough about one another's problems to understand them and to maintain the same scientific and dispassionate attitude which the doctor is taught to use in dealing with disease.

Each individual cell has a part to play in the beautifully adjusted mechanism of the human body. Any dysfunction in a group of cells or an organ of the body brings symptoms in remote parts or in the whole organism. In a comparable manner the unnecessary illness of any person in modern society, or of any group of the population has a direct relationship to the function of the society in which he is a part. The excess of illness among the poor, the lack of good medical care, the continued prevalence of preventable disease, the unnecessary loss of life, all are of importance to society as a whole.

Half of all illness is among the very poor, it has been found in the recent National Health Survey made by the Public Health Service. Twenty-five per cent of all illness is in families on relief; another 25 per cent is among families whose total income is less than \$1,000 a year. It is estimated that more than half a million persons in the United States—and three-quarters of them heads of families—are unemployable because of accident or disease, much of it preventable. Further, 80 per cent of all unemployable heads of families are either on relief or in the group having less than \$1,000 annually. This is a ratio of one in every 20 in the relief and low income classification as compared with one in 250 similarly disabled among those in more comfortable circumstances.

The community pays for preventable disease and disability. It pays in relief of the unemployables, in pensions and in institutional care. It would be cheaper for us as a nation to spend more for the prevention and cure of disease than to continue to bear its money cost. It is, therefore, not only the humane but the practical considerations which bring to our attention the acute need for dealing courageously with unnecessary sickness in this country. Our efforts up to now have been sporadic, half-hearted, and

frequently unscientific. The time seems opportune for the best minds in the medical profession to consider how medical knowledge can best be brought to fuller use by all of the people—how we may take up the lag between what we know and what we do. It should be possible for a national health program to be evolved which would be adapted to the varying needs of each state and community.

A practical program to utilize our scientific resources for life-saving would bring advantages to our profession almost as great as to the population which would be served. Among other things, it would go a long way toward ousting the quacks and cults and unqualified practitioners of medicine. One does not find them in the Scandinavian countries, for example, where medical service is available both to those who can pay well and those who can pay a little and where medical service is so uniformly good as to be universally trusted. Moreover, a well-rounded national health program would solidify the forces of public health and the forces of medical practice which, after all, are but the two useful arms of the greatest of sciences. And finally, such a program would inevitably restore to the medical profession the trust and confidence of all the people, would wipe out the disaffections which have arisen because medicine has been misinterpreted to the people. Our best and greatest leaders in clinical medicine have been modest and reticent. Our wordiest spokesmen have not interpreted the humanities which are the foundations of medicine. They have made it a defensive thing, a trade union. They have failed, in the minds of many lay people, to identify the common good as the first interest of medical organization.

In approaching this problem it is my opinion that we should not continue to think in terms of the separateness of public, private and voluntary efforts to prevent and cure disease. There is an interrelationship, even a unity of the several parts. Whether we consider the doctors, the dentists, the nurses, the pharmacists, the hospitals, the laboratories, the social welfare and relief agencies, or the public health departments, we must realize that each exists because each has a part to play. We need a united effort—a supreme effort from every integrated factor—if we are to bring better health to more of our people.

I would suggest that our objective in part should be more medical care and health service for those unable to procure it for themselves. An equally important objective, however, is constantly to improve the quality of medical care for this and other groups of the population.

Health insurance, per se, does not either prevent disease or improve the quality of care. Its cost bears most heavily upon the small wage-earner least able to pay. The collection of premiums from any except industrial workers is difficult, if not impossible. Health insurance assumes the continued existence of the current volume of illness as unavoidable and merely spreads its cost. Nowhere does it provide for such expensive and long-continued treatment as is needed in tuberculosis and mental disease. Even venereal disease treatment is not included in most existing insurance

schemes. It cannot embrace the groups on relief, because they have nothing to contribute. Public taxes must take the place of insurance contributions for them and must supplement the contributions for the entire low-income group, or else another system must be worked out for their care.

It is for these reasons that I disagree with those who look upon health insurance as a cure-all for our admitted deficiencies in protecting the health of the people. To my mind health insurance in its most successful existing form will make very little impact upon the actual amount of disease in our population. Whether we have health insurance or not makes very little difference, I think, to our great basic problem of saving life and reducing disability.

A line of progress sounder than health insurance has seemed to me to consist of applying the knowledge we now have for the prevention and control of those great causes of disease and death against which there are scientific weapons of unquestioned power. To do this requires no radical revision of medical practice, no standardized program for every township health officer and county medical society. We need only to build better and more wisely in the patterns we now have. We need to mobilize the forces now in the field but with leadership so scattered, with such vagueness of purpose, and diversity of direction as frequently to obstruct state and national progress in health rather than to advance it. I firmly believe that every health organization should have local control and that every health program should be built on the specific needs of the community it is designed to serve. But unless we do have a health organization in every community, unless the leading doctors in each state are interested enough to set its standards and the state health department is competent to supervise it, unless the state has federal leadership and financial assistance as merited, we shall never have a national health effort against the great plagues of our day.

In many areas, particularly the rural areas, there is a serious shortage of hospital and other physical facilities for good health. Many whole states have practically no beds for tuberculosis, and scarcely the beginnings of a case-finding program. Many areas lack essential laboratory facilities. Mental hospitals frequently are only over-crowded warehouses for the storage of the wrecks left by mental disease. There is a shortage of nearly 200,000 general hospital beds, yet through community bad management hospital beds stand empty in many of our cities.

For those on relief and otherwise unable to support themselves, we should substitute for our present haphazard practice of inadequate care, or no care at all except by the generosity of the doctor, a minimum standard of general medical, nursing and hospital service paid from public funds and given as a matter of right and not of charity.

For those in the marginal economic groups we should supplement what they can do for themselves by public aid in providing the expensive diagnostic and treatment services necessary in obscure conditions and catastrophic illness. The same yardstick used in measuring the need of these

underprivileged for food and shelter is not a measure of their ability to provide for sudden, serious illness. The yardstick should be what the individual needs to restore him to health and competency. He should not be degraded by the pauper's oath because sickness has struck him or his family.

Local responsibility and action should be encouraged to the extent that local resources are available. It would seem wise, also, to use federal funds for these purposes to the extent needed to insure minimum standards and to equalize the financial burden between the states.

In such a plan the medical profession itself should be made responsible for prescribing the standards of service and enforcing good professional conduct. There should be a constant effort to improve the quality of medical service. Better financial and professional opportunities are necessary if medicine is to grow as an instrument for public welfare. A grateful public would be anxious that the profession share in the additions to our national income which are inevitable from a more healthful citizenship.

All of these aims are realizable. All can be accomplished without any basic change in our present system of medical practice. The suggestions which I have ventured to make represent no new or untried action. They represent only an extension, on a scale adequate to meet the needs, of methods and actions which now are in operation.

It is true that if the economists were able to show us how to produce and distribute an income adequate for the health and other needs of every family, the need for many of the measures I suggest would be minimized. The inter-relationship between poverty and disease is well known. Disease begets poverty which in turn creates further disease. Our ability to prevent disease far exceeds our ability to control causes of poverty. Medicine and public health, therefore, should lead rather than follow. Its application offers the best opportunity to interrupt the downward spiral, to tear out the roots of poverty and its companion, ignorance, by attacking its one real preventable factor. Medicine can give hope and confidence to an age almost despairing that man's intelligence will keep us from reverting to barbarism.

In these days of international marauders, when force replaces reason, when hate rather than human understanding rules the mind of man; in these days when well-meaning citizens, otherwise rational beings, allow passions and prejudices to dominate even the domestic scene; in these days when the economists and statesmen seem uncertain of what is the clear road ahead, let us, the doctors and the scientists, not sit idly by. We are all aware that for many diseases we have scientific weapons of unquestioned power. Give us the means of using them for every citizen. Give every man or woman born an American an equal birthright of health. The objectives are clear. There is no serious disagreement as to method. Let us admit with equal frankness that for many diseases and conditions we have imperfect knowledge. Give us means to extend it,—freedom to seek the truth and the will to pursue it.

CASE REPORTS

HYPERPARATHYROIDISM WITH RATHER RAPID RECALCIFICATION OF BONE FOLLOWING THE REMOVAL OF AN ADENOMA*

By THOMAS P. SPRUNT, M.D., F.A.C.P., *Baltimore, Maryland*

THE body's calcium is obtained of course from the food. Its absorption from the intestinal tract is aided by vitamin D. In the blood stream the amounts of calcium and phosphorus are maintained at the so-called normal steady level as physiological constants by the activity of the parathyroid glands which govern the deposit or the resorption of calcium and phosphorus from the storehouses in the bones. The bones therefore play an important part in the metabolism of these elements in addition to furnishing the rigidity of the skeleton and spaces for the bone marrow or blood building organs.

We have recently become acquainted with the fact that with the growth of a functioning adenoma of parathyroid tissue and the presence of a great excess of this material there may develop a state of chronic hyperparathyroidism, the essential clinical features of which may be described under three general categories. First, there is the excessive withdrawal of calcium from the bone with a demineralization of bone, fibrous replacement and the development of cysts and giant celled tumors or osteoclastomata. There are pains and aches in the body and extremities and perhaps fractures through the cysts or other weakened portions of the bone. Second, the hypercalcemia or excessive amount of calcium in the blood which is associated with a hypophosphatemia may be linked with the muscular hypotonia, relaxation of the joints, flat feet, lassitude, fatigability and malaise. Third, the hypercalcinuria, or excessive excretion of calcium in the urine, may result in a polyuria or a tendency to the formation of renal stones and to damage of the kidney itself from calcium deposits in the renal tissues.

It has been demonstrated repeatedly that after the removal of the excess parathyroid tissue by excision of the tumor, the process is reversible and the patient can be cured provided no marked bony deformities have occurred and the kidneys have not been greatly damaged.

The case I have to report presents a number of interesting features.

CASE REPORT

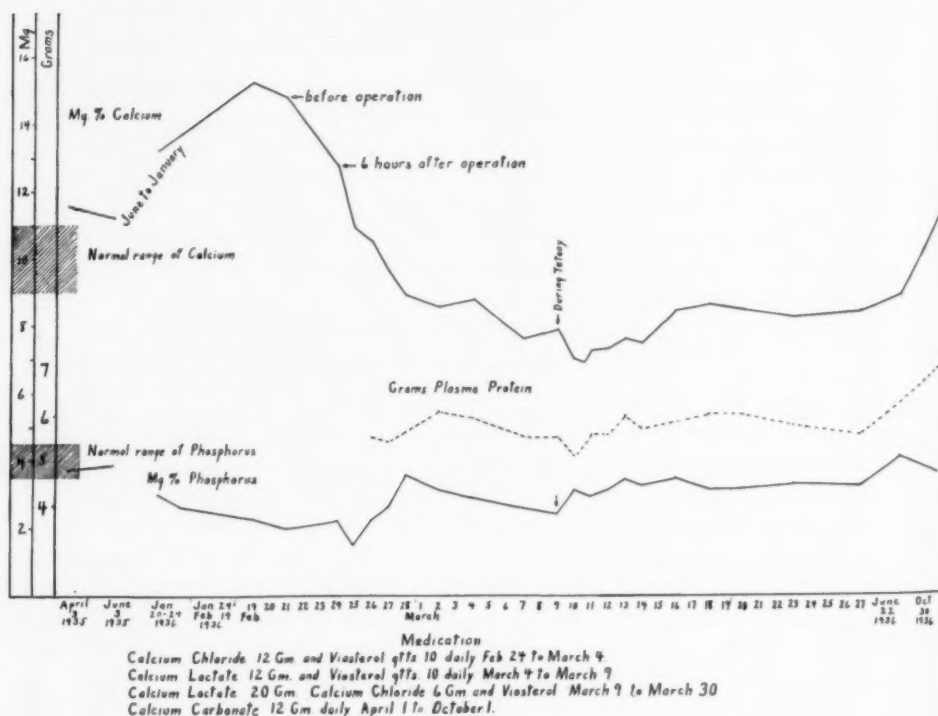
The patient was a woman, 54 years old when we first saw her in April 1935. She had never been robust. She had three children and while nursing the second child, 16 years before, she had suffered an attack of manifest tetany that was satisfactorily treated with calcium. Evidences of latent tetany persisted for some time. We may assume that under conditions demanding unusual amounts of calcium, her food supply was deficient in this element, or perhaps more probably there was a lack of vitamin D resulting in a low blood calcium level and the symptoms of tetany. We

* Received for publication September 7, 1937.

have here a satisfactory setting for a more or less prolonged stimulation of the parathyroid apparatus in the effort to compensate for this deficiency. Perhaps, as Wilder assumes, there were cell rests with parathyroid potentialities that received their stimulus to development at this time and later grew into a functioning parathyroid adenoma.

Nine years ago, the menopause was induced by roentgen-ray. There was at this time a sharp but short depression.

The onset of the present illness was insidious. The date cannot be determined but for several years there had been increasing fatigability, lassitude, continuous



CASE OF HYPERPARATHYROIDISM

Woman, aged 54 years, complained of aching in hips, legs and knees, stiffness and difficulty in walking, malaise, fatigue. Mother of 3 children. Tetany while nursing second child 16 years ago. "Nervous breakdown" 9 years ago. Increasing disability past few years. Fracture left wrist September, 1933, and again January, 1934.

CHIEF CLINICAL FEATURES

General. Hypercalcemia; hypophosphatemia; lassitude, weakness, fatigability, muscular hypotonia.

Bones. Pain in chest, knees, feet and legs; flat feet; general rarefaction of bones with cysts or giant celled tumors in skull, ribs, jaw, pelvis, fingers, arm and leg.

Kidneys. Mild polyuria; fixed low specific gravity; reduced phthalein excretion; slight arterial hypertension.

Operation. (Dr. Rienhoff), February 24, 1936. Removal of parathyroid adenoma 2 cm. in diameter.

Postoperative Course. Prompt fall in serum calcium; tetany on 15th postoperative day. Slow gradual symptomatic improvement continuing throughout the 8 months. Rather rapid general recalcification of bones and filling in of all local lesions except one phalanx. Dense calcification of lesions after 4 months. More nearly normal bone after 8 months.

aching in the hips, legs and knees with difficulty in walking and stiffness now in the feet and then in the knees. In September 1933, and again in January 1934, there had occurred fractures of the left forearm from falls on the floor in her home. In June of 1934, weakness increased and shakiness began so that she could not knit on account of the tremor. She was comparatively comfortable in bed but was never entirely free from pain. She had been given full doses of thyroid for a period but none since August 1934. She had received a good deal of calcium until October 1934, but none from this time until after the operation 18 months later. Her appetite was poor, she was nervous with occasionally mild depression, but slept well. She was sensitive to cold. There was no constipation.

Physical Examination: She was rather tall, five feet, eight inches in height and weighed 136 pounds. Her gait was uncertain, weak and rather awkward. She could not rise from a sitting position in a chair without using her hands to help push the body upward. In the standing position the posture was fairly good with the exception of a slight upper thoracic kyphosis. There was a slight deformity just above the left wrist, the site of fractures some months before. There was no definite tenderness of bones or of joints, which were negative on general physical examination with the exception of mild crepitus in the knee joints. The muscles were flabby and atonic. The neurological examination was negative. The pulse was regular, rate 76. Blood pressure 130 mm. of mercury systolic and 90 diastolic. The thyroid gland was palpable with a rather full isthmus and right lateral lobe which was somewhat nodular. The skin was rather dry.

There was a refractive error but otherwise the eyes were normal.

Roentgen-ray examinations showed in the lateral view of the spine some sharpening of the points of the vertebrae and one vertebra near the mid portion of the thoracic spine that was wedge-shaped, suggesting a mild compression fracture. The bones of the thoracic and lumbar portions of the spine and of the pelvis appear somewhat rarefied. Films of the left hand and wrist showed a well healed fracture of both radius and ulnar bones. The lateral view of the skull showed a normal sella turcica. There was no striking rarefaction of the bones of the calvarium. Films of the teeth were not remarkable.

Laboratory Tests: The basal metabolic rate was retarded, minus 17 per cent, minus 20 per cent. There was a moderate secondary anemia with red blood cells 4,000,000, hemoglobin 70 to 75 per cent, white blood cells 8,300 with a normal differential count. The blood Wassermann reaction was negative. Stools were normal. The urine showed a rather low specific gravity, 1.008 to 1.010, with a trace of albumin and very few casts. The gastric analysis and examination of the cerebrospinal fluid had been done elsewhere and were normal. Chemical tests of the blood revealed a fasting blood sugar of 98 mg. per cent, non-protein nitrogen 32.5 mg. per cent, blood uric acid 4.7 mg. per cent, blood calcium 11.6 mg. per cent, and blood phosphorus 3.8 mg. per cent.

The diagnosis of hyperparathyroidism was not made at this time. The rarefaction of the bones was enough to be noticed in an objective description of the roentgen-ray films but was not marked. The blood chemistry was practically normal. The value for calcium at 11.6 mg. per cent may be considered a little high but the phosphorus at 3.8 mg. per cent was quite normal. The patient remained under our observation from April 12, 1935, to June 23, 1935, with a general rest and upbuilding plan of treatment, during which she gained 20 pounds in weight but only slightly in strength and feeling of well-being. The blood counts at times were as low as 3,700,000 red blood cells and 70 per cent hemoglobin, and this secondary anemia did not respond favorably to treatment until after large doses of iron and of liver had been given. From one to two grains of thyroid were given each day and the basal metabolic rate increased to the lower levels of normal. Roentgen-ray films of the bones in June showed no striking changes from those taken previously. The blood

calcium at the end of this period was 11.2 mg. per cent and the blood phosphorus 3.9 mg. per cent, practically normal values.

We saw the patient again on January 20, 1936. There had been no great change in her symptoms. She felt that in some respects she was a little better but the aching was as severe and although she walked better, she found it difficult to get up from a chair and the discomfort in the knees was worse. Fatiguability and lassitude persisted. She was very nervous and at times quite weepy. She gave the additional interesting history that in September of 1935 an operation had been performed for a cyst of the jaw by which she had lost three teeth.

The physical examination was quite similar to that of 10 months before. The height was the same, 5 feet, 8 inches, and the weight 143 pounds. The blood pressure had increased to 150 systolic and 90 diastolic. The gait was about the same as before. The musculature of the legs seemed generally weak and she spoke of a feeling of insecurity about the left wrist.

The roentgen-ray films taken at this time and others taken a month later were quite illuminating.

The thoracic and lumbar portions of the spine showed no striking changes from the films of the year before except perhaps for some increase in the decalcification. The film of the pelvis showed definitely increased general rarefaction of the bones and this was particularly striking in the cancellous portion of the upper third of each femur. In the left ischium there was a very distinct round clear area that measured about $1\frac{1}{2}$ by 1 cm. There were other less definite localized cyst-like areas, one in each ilium and one in the head of the right femur.

The ribs and clavicles in general were moderately rarefied and there were large fusiform lesions, one on the seventh right rib and another on the ninth left rib. There were other small, less sharply defined localized areas of rarefaction in the ribs and the upper ribs on each side showed a moth-eaten appearance of the outer border particularly on the superior surface.

Other films of the chest and of the pelvis the following month showed little change during this period. Roentgen-ray films of the arms in February showed the long bones distinctly rarefied with rather thin cortex and porous cancellous portions. Just above the site of the old fracture of the left wrist there was in the left ulna a large lesion expanding the outlines of the bone and with a very thin cortex around it. This lesion measured about 5 by $1\frac{1}{2}$ cm. and was crossed by bony trabeculae.

The bones of the hands showed increased radiability. The phalanges of the right fore-finger showed the only localized lesion. The middle phalanx was a mere shell with a very thin cortex around it. The distal portion of the proximal phalanx contained a cyst-like area which measured 1 cm. by 8 mm. A film of the left shoulder showed rarefaction in the humerus, in the scapula and in the clavicle as well as in the ribs. The lateral view of the skull taken in February showed a fine mottling involving the bones of the whole calvarium. There were three small clear cyst-like areas in the parietal region, one of them about 1 cm. in diameter and the other two slightly smaller. The tables of the skull appeared a little broad in the fronto-parietal region.

The femora showed no marked changes except near the ends of the bones where the general rarefaction was noticeable. The tibiae showed a certain degree of general rarefaction as well as the fibulae. There was a small sub-cortical clear cyst-like area in the right tibia surrounded by an area of increased density. A hand's breadth above the ankle the left tibia showed a thin cyst-like area, apparently in the cortex in the anterior portion of the bone. This was long and narrow, measuring about 2 cm. by 5 mm. The bones of the feet showed general rarefaction but no localized lesions.

Roentgen-ray films of the kidneys showed that the kidney shadows were of normal size and in normal position. There was no suggestion of a stone in the

region of the pelves, ureters or bladder. There was no definite calcification in the region of the kidneys with the possible exception of one small speck about the size of a pin head in the left kidney.

Laboratory Tests: The basal metabolic rate was approximately the same as ten months previously, minus 18 per cent, minus 19 per cent, although the patient had continued to take a one grain tablet of thyroid daily.

The blood count was now normal. Stool examination negative. Urine showed low specific gravity, a trace of albumin and a few casts.

The blood calcium was 13.2 mg. per cent and the blood phosphorus 3 mg. per cent. A repetition of this test a few days later showed the calcium 13.7 mg. per cent and the phosphorus 2.7 mg. per cent. Further studies of the urine showed a mild polyuria with an output of about two liters a day, with low fixed specific gravity and a slightly reduced phenolsulphonephthalein output, 35 per cent in two hours. Tests for Bence-Jones proteinuria were negative. The non-protein nitrogen of the blood was normal.

The diagnosis of hyperparathyroidism was now clear and the patient readily consented to an exploration of the parathyroid region in the hope that a tumor might be found and removed.

In summary there were: (1) a typical picture of *osteitis fibrosa cystica* with generalized rarefaction of bones, with definite evidence of cysts or giant celled tumors in the skull, ribs, ulna, phalanges, pelvis, femur and tibiae. There was the history of a cyst of the jaw having been treated a few months before and of two fractures of the left arm two years or more ago. There were pains and aches in the bones and soft parts.

(2) There was definite hypercalcemia, the calcium reaching 15.2 mg. per cent before the operation; definite hypophosphatemia with a value of 2.3 and later 2 mg. per cent. Associated with these features were the weakness, lassitude, fatigability and muscular hypotonia.

(3) There were signs of a renal disturbance in the mild polyuria, with urine of low specific gravity, trace of albumin and a few casts, reduced phenolsulphonephthalein output, but no evidence in the roentgenograms of calcification of the kidney nor of renal stone.

The operation was performed on February 24, 1936, by Dr. William F. Rienhoff, Jr. On lifting the left lobe of the thyroid gland there was found behind it a round mass, 2 cm. in diameter, gray in color, smooth and soft, attached by separate blood supply but loosely to the lower pole of the thyroid gland. This tumor was removed with the exception of a small portion that was left in situ and another small piece that was imbedded in the sternocleidomastoid muscle, in order to minimize the danger of postoperative tetany.

Subsequent histological examination of the mass showed a very cellular tumor, the cells quite uniform in size and of polyhedral shape. The nuclei were round or ovoid with evenly dispersed chromatin granules. The nuclei varied only slightly in size but there were a few giant forms. No mitotic figures were noted.

Postoperative Course: The output of urine decreased from 2,000 c.c. the day before operation to 350 c.c. the day after operation. Subsequently the amount of urine gradually increased until three or four weeks following the operation it had reached almost three liters a day, a figure distinctly higher than the pre-operative level. The specific gravity remained low but the phthalein excretion at this time was 50 per cent in two hours.

The blood calcium fell promptly. On the evening of the operative day it was 12.8 mg. per cent and the next day 10.9 mg. per cent. Twelve grams of calcium chloride were given daily by mouth until March 4, when a sharp decrease in the carbon dioxide combining power of the blood suggested a change to calcium lactate, 12 grams a day by mouth. A few days later, on March 9, the fifteenth postoperative

day, there occurred a manifest attack of tetany (blood calcium 7.9 mg. per cent) that was treated satisfactorily by means of calcium gluconate intravenously. Following this episode the daily dose of calcium was increased to 20 grams of calcium lactate and 6 grams of calcium chloride. This was continued until April 1, after which 12 grams of calcium carbonate were taken daily for six months. Ten drops of viosterol were given daily until the summer months when sun baths were substituted.

During the postoperative period the anemia had recurred and this was treated by means of ferrous sulphate and liver extract.

On March 21, the basal metabolic rate was minus 27 per cent and a one grain thyroid tablet each day was prescribed.

The symptomatic improvement following the operation was slow and quite gradual but has continued throughout the eight months since the operation and has now reached a very satisfactory level. The patient walks and moves in general with a great deal more feeling of freedom. She rises from a chair without the assistance of her hands and she states that she feels better than she has felt for at least ten years.

The recalcification of the bones has been prompt and gratifying. Histological examinations in other cases have shown that immediately following the removal of the parathyroid adenoma the excessive activity of the osteoclasts ceases and the rebuilding of bone begins. This is, however, as a rule not appreciable in roentgen-ray films for several months. In this case the recalcification of the bones was slight but noticeable four weeks after the operation. Four months after the operation there was a marked improvement in the general calcium content of the bones as judged by the roentgen-ray films and almost complete filling of all the localized lesions by deposits of calcium. At this period the appearance of the roentgenograms suggests that larger amounts of calcium have been deposited in the sites where the lack of it was greatest. The calcium deposits are dense after four months in the two large lesions in the ribs, in the phalanges of the right fore-finger and in the round cyst-like area in the ischium.

Roentgen-ray films taken eight months after the operation show a further recalcification of the bones in general and there is now the appearance at the site of the former localized lesions of more nearly normal bone, somewhat less densely calcified than in the films taken four months after the operation.

The latest check of the blood chemistry in this case showed calcium 11.3 mg. per cent and phosphorus 3.6 mg. per cent. These figures may be accepted as normal although the figure of 11.3 for the calcium may appear a little high. It may be considered, however, in connection with the finding of the value of 7 gm. per cent for the total plasma proteins, a figure higher than previously obtained in this case. On consulting the chart prepared by McLean and Hastings, it may be seen from their calculations that with a blood plasma protein of 7 gm. per cent and calcium of 11.3 mg. per cent the ionized calcium is approximately 5.05 mg. per cent. It is supposedly the ionized calcium that is of importance in parathyroid disease.

COMMENT

Since Mandl's demonstration of change in metabolic abnormalities following the operative removal of a parathyroid adenoma in 1925, a fairly large number of cases has been reported. Wilder and Howell, in their recent review of the literature, state that they are willing to accept 135 definitely proved cases since the date of Mandl's publication. These authors point out the apparently very unequal distribution of this disease geographically with a relatively large number of patients being reported from the North Atlantic states, especially Boston.

The features of special interest in the case here reported include: (1) The definite history of a disturbance in calcium metabolism with an inadequate supply of calcium and manifest tetany about 17 years before the operation. This fur-

nishes a possible or even quite probable basis for a stimulus to parathyroid over-activity and it seems probable that during this period the embryonic cell rests with parathyroid potentialities received the stimulus that resulted in the growth of an adenoma.

(2) The variations from time to time in the intensity of the metabolic disturbance are obvious. These variations during our periods of observation within the space of a single year were such that at the first opportunity a diagnosis could not be made and 10 months later all signs were well marked. The disease, however, certainly goes much further back than the time of our initial examination for there is the history of fractures of the left fore-arm 18 months before we first saw the patient. While these fractures were not necessarily pathological fractures, yet in view of subsequent events it seems highly probable that they were. The general symptomatology, too, that is quite characteristic also in the light of after events certainly goes back for several years. Thyroid feeding may add materially to the decalcifying process in the bones but it seems unlikely that our prescription for thyroid changed the course in this case greatly for she had been receiving thyroid medication at intervals during the past several years. A possible partial explanation of the more rapid progress in the *osteitis fibrosa cystica* during 1935 may lie in the cessation of the calcium therapy which she had taken frequently during the preceding several years. It has been shown by Albright and others that feeding of calcium retards the decalcification of the bones in *osteitis fibrosa cystica* but perhaps renders the patient more liable to renal complications.

(3) The symptomatic recovery or improvement was much less dramatic than is often described. It was, on the other hand, slow and gradual but just as gratifying ultimately after a period of eight months.

(4) The recalcification of bone in this case seems definitely more rapid than that usually described. This may be due in part to the full doses of calcium taken by mouth over the period of seven months following the operation. Viosterol was taken during several of these months and sun baths during the summer. In regard to the recalcification of the localized lesions it is said usually that giant celled tumors recalcify satisfactorily and that cysts do not. There is no clinical criterion by which cysts can be certainly distinguished from tumors. In this case all localized lesions have recalcified with the exception of a portion of one lesion in the phalanx which is not yet filled after eight months. The roentgen-ray appearance of these local lesions after four months is certainly that of a relatively disorganized and heavy mass of calcium deposit surrounded by a very narrow rarefied line that enables one to recognize the lesions readily. In the films after eight months these lesions are less easily distinguished from the surrounding bone and the bony structure within them seems definitely more nearly normal.

REFERENCES

1. WILDER, R. M., and HOWELL, L. P.: Etiology and diagnosis in hyperparathyroidism, Jr. Am. Med. Assoc., 1936, cvi, 427-431.
2. McLEAN, F. C., and HASTINGS, A. B.: Clinical estimation and significance of calcium-ion concentrations in the blood, Am. Jr. Med. Sci., 1935, clxxxix, 601-613.
3. ALBRIGHT, F., AUB, J. C., and BAUER, W.: Hyperparathyroidism, Jr. Am. Med. Assoc., 1934, cii, 1276-1287.

PRIMARY CARCINOMA OF THE JEJUNUM; REPORT OF A CASE *

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PRIMARY carcinoma of the jejunum is of exceedingly rare occurrence. From the case reports of various European and American clinics, the incidence of primary carcinoma of the jejunum varies from 0.3 per cent to 1.0 per cent of all carcinomata involving the gastrointestinal tract from the cardiac end of the stomach to and including the rectum. Carter,¹ reviewing the literature up to 1935, found less than 100 cases reported of primary carcinoma of the jejunum discovered at operation, although a considerably larger number of necropsy cases had been reported. In the files of the Mayo Clinic prior to June 1936, Nettrour² found 31 proved cases of this entity, including both the operative and necropsy cases. As reported also by Rankin and Mayo,³ carcinoma of the large bowel, including the cecum and rectum, was found in this clinic 80 times as frequently as carcinoma of the small bowel. Of the cases of carcinoma of the small bowel, 38 per cent occurred in the jejunum. A surprising number of these were at, or a short distance from, the ligament of Treitz.

In a series of 41,883 autopsies at the Vienna General Hospital including 343 cases of intestinal carcinoma, Johnson⁴ was unable to find a single case of primary carcinoma of the jejunum.

Raiford⁵ in 1932 collected from the literature 339 benign and malignant tumors of the entire small intestinal tract, and reported 88 cases among 56,500 surgical and autopsy specimens from the Johns Hopkins Hospital; the malignant tumors included 3 surgical cases of primary jejunal carcinoma.

Further emphasis was laid on the rarity of this lesion in 1930 by Newton and Buckley,⁶ who in summarizing the reported statistics of European clinics and adding personal reports from eight of the largest hospitals in this country, listed only 35 histologically verified cases among 135,000 autopsies.

Since the opening of the Roosevelt Hospital in New York in 1871, according to Cave,⁷ only three specimens of carcinoma of the jejunum are entered in the laboratory files.

Pathology. Primary carcinoma of the jejunum is practically always, histologically, of the adenomatous type. By far the most common in occurrence is the annular, constricting variety, the other rarer type being the polypoid, ulcerating and non-constricting lesion.

Metastases occur late. In Rankin and Mayo's³ series, serious metastatic involvement of the peritoneum and lymph nodes was found at operation in one-third of the cases. The mesenteric lymph nodes and peritoneum are usually first involved, then the liver, lungs, long bones and spinal dura in order. In the cases reviewed by Carter,¹ the mesenteric lymph nodes were enlarged in 75 per cent of the cases. In his opinion, further enlargement of the retroperitoneal nodes does not necessarily mean malignant extension nor do they preclude the advisability of radical resection, as the nodes may be inflammatory.

Symptoms. From a review of the cases reported it would appear that the onset of symptoms is most insidious and the duration quite variable, being from

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two or three months to five years or more. The types of symptoms presented are in direct relation to the degree of intestinal obstruction produced and the existing anemia. With non-obstructing lesions the early symptoms are usually those of weakness, weight loss, and easy fatiguability, due, presumably, to the gradual loss of blood and interference with the normal absorptive power of the small intestine. In all cases loss of weight has been a constant finding. Rankin reported an average loss of 28 pounds in his series.

A mild or moderate secondary anemia usually exists even in the earlier cases, the blood loss being occult in character and rarely are tarry stools reported. This, of course, is accounted for by the absence of an ulcerative stage in the development of the majority of the growths encountered.

Pain is not a symptom of frequent occurrence in the case reports of lesions found at or near the ligament of Treitz. Distention of the duodenum and first portion of the jejunum apparently occurs without producing the characteristic cramp-like pain complained of in obstruction resulting from intrinsic lesions of the ileum and colon. The character of the pain, however, varies with the degree of existing stenosis. It is usually localized in the region of the umbilicus, as is somewhat characteristic of other lesions of the small bowel, and may be sharp or dull and may seem to shift about somewhat in the abdomen, accompanied by borborygmus. Steady pain in the epigastrium is a late symptom and probably results from metastasis to the retroperitoneal lymph nodes. The onset of pain bears an inconstant relationship to the intake of food or alkalies.

In keeping with the insidious onset and long duration of symptoms in many instances, the attacks of pain are often followed by long periods of remission, the obstruction of the lumen apparently subsiding temporarily, leaving the patient free of discomfort during the interim. As the disease advances, however, exacerbations occur more frequently and sooner or later nearly all cases develop nausea and vomiting.

The time of onset of vomiting depends primarily upon two factors, the degree of existing obstruction and the proximity of the obstructing lesion to the pylorus. Carter,¹ in a review of 30 cases reported from 1927 to 1935, found vomiting to be a clinical feature in 28 cases. The vomiting may be profuse if the stenosis is high, and the vomiting of large amounts of grayish green fluid containing bile and particles of undigested food is typical of obstruction near the ligament of Treitz. This type of vomiting is observed in a large percentage of late cases and constitutes one of the most characteristic symptoms. The absence of fecal vomiting is also significant.

Varying degrees of constipation are reported, sometimes with alternating periods of diarrhea.

Physical Findings. In the early stages there is an absence of positive findings on physical examination. Later, an evident loss of weight and the pallor of the secondary anemia manifest themselves. Abdominal distention, in contradistinction to that seen in obstruction involving a more distal portion of the bowel, is usually very slight or absent. Visible and reverse peristalsis may be present. An abdominal mass is usually not palpable until after metastasis occurs.

Diagnosis. Clark,² in 1926, found that an early diagnosis of carcinoma of the jejunum had not been made in any of the cases reported up to that time, due probably to the absence of tangible clinical symptoms and positive roentgen-ray findings. The roentgenologic diagnosis depends upon the presence of obstruction

and no case report was found in which even a roentgenologic diagnosis was made before obstruction occurred.

Primary carcinoma of the jejunum occurs in persons relatively younger than those in whom carcinoma develops elsewhere in the intestinal tract. The decade of greatest incidence is the age period between 30 and 40, and men are affected twice as frequently as women.

The fact should be kept in mind that pain arising from lesions of the small bowel is more or less characteristically referred to the region of the umbilicus and that it usually bears some inconstant relationship to the taking of food.

All cases with beginning cachexia or gastrointestinal disturbances associated with the persistent and unaccountable finding of occult blood in the stools, merit a thorough roentgen-ray study of the entire small intestinal tract, with the thought in mind of a possible malignancy in this portion of the bowel. This consideration is of prime importance, particularly in those instances in which the bleeding is unaccounted for after a double-contrast barium enema study and sigmoidoscopy.

In the presence of the vomiting of large amounts of bile-stained fluid, as previously described, the diagnosis should always be suspected. Pyloric stenosis may be closely simulated.

In spite of suggestive symptoms and clinical signs, roentgenologic findings afford the only early positive preoperative diagnostic criteria. A preliminary flat plate of the abdomen may prove of value in demonstrating dilated loops of small bowel, thus indicating an obstructive lesion somewhere above the ileocecal valve. Under normal conditions, except in infancy or in cases where the ileocecal valve is incompetent, the roentgen-ray should not reveal gas in the small bowel.

The roentgen-ray diagnosis depends upon the presence of obstruction, which in itself precludes the advisability of administering barium by mouth except with caution. A serial study at hourly intervals with a small barium progress meal is, of course, the preferred technic when this lesion is suspected. Any delay in the emptying of the small intestine beyond 10 hours should arouse suspicion. In those few cases reported in which the diagnosis was made preoperatively, there was shown by roentgen-ray delayed emptying of the stomach, dilatation and atony of the proximal jejunum or duodenum, or stenotic peristalsis in the occluding type. Rarely has a frank defect in outline of the jejunum been demonstrated.

Treatment. Radical resection with an end-to-end or side-to-side anastomosis is the surgical procedure of choice in these cases. Palliative side-tracking operations are indicated if this is inadvisable. Postoperative roentgen-ray therapy is justifiable.

Radical resection resulted in a mortality of 36 per cent in 70 cases of carcinoma of the jejunum or ileum reviewed by Hellström.⁹ The immediate mortality, however, was 70 per cent in those cases in which operation was performed during the stage of acute obstruction and only 18 per cent in those cases in which operation was done when no acute obstruction was present.

Prognosis. The follow-up results in the cases in Hellström's series showed a definite cure in 16 per cent. However, no patient in Rankin and Mayo's series lived more than three years and the duration of life after the diagnosis was

established ranged from one month to three years, the average being less than a year.

By means of improved roentgen-ray technic, the establishment of an early diagnosis in primary carcinoma of the jejunum, it is to be hoped, will make possible a larger number of radical resections with cure, since distant metastasis is apparently relatively uncommon.

CASE REPORT

W. B., white male, aged 35 years, salesman, married, was admitted to the Medical Ward of the Presbyterian Hospital on July 30, 1936. The patient was working regularly up to the time of admission. The presenting complaints were extreme weakness, loss of 10 pounds in weight in the past three months, tarry stools, and a very



FIG. 1. Primary carcinoma of the jejunum, 20 centimeters distal to the ligament of Treitz.

occasional pain, for the past nine months, just above the umbilicus, without relationship to food-intake, but relieved by alkalis. Appetite was good and there was no history of nausea. There had been vomiting on one occasion only, three days before admission, following the drinking of a large amount of wine. The past medical history was insignificant except for the existence of moderate constipation for the past two years.

The family history was interesting, in that the patient's mother died of some type of intra-abdominal cancer, and a sister died of cancer of the uterus.

Physical examination was essentially negative, except for marked pallor of the skin and mucous membranes; a systolic blood pressure ranging between 90 to 100 mm. of mercury, and a very slight degree of tenderness on deep palpation midway between the xiphoid process and the umbilicus. No mass was palpable in the abdomen. The liver and spleen were not palpable.

The Wassermann and Kahn tests were negative. Routine blood chemical tests gave normal results. The blood count on admission revealed a hemoglobin of 52 per cent, red blood cells 3,740,000. Fractional gastric analysis showed a grade I hyperchlorhydria, but no fasting retention and no blood. All stools were strongly positive for occult blood. Sigmoidoscopy failed to reveal any source of bleeding.

In view of the location of the pain, the relief obtained with alkalies, the hyperchlorhydria and the persistence of tarry stools, a tentative diagnosis of bleeding duodenal ulcer was made, roentgen-ray studies being postponed until diminution of the bleeding occurred.

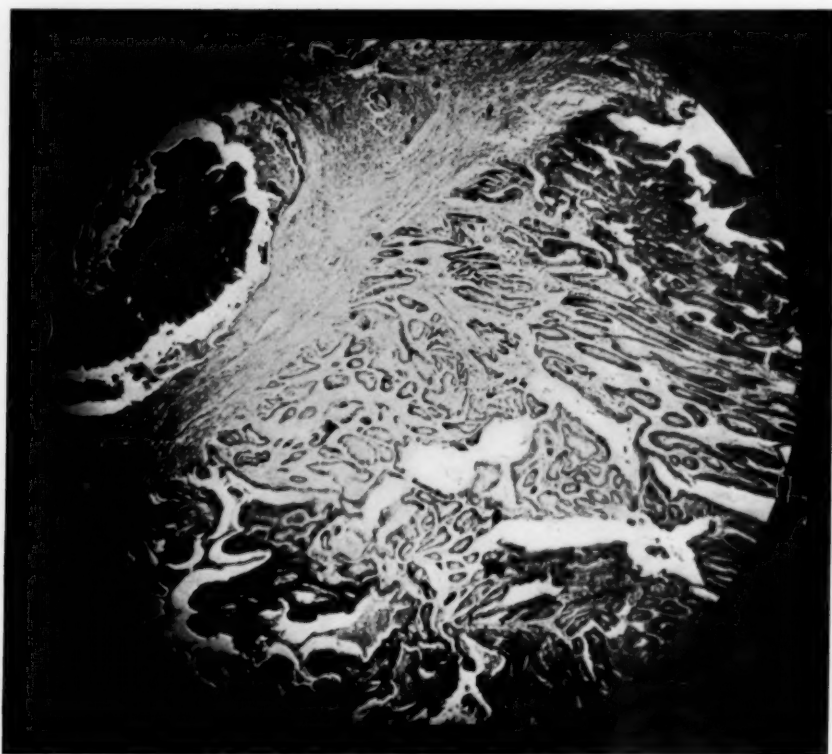


FIG. 2. Section of the tumor mass, reduced from a photomicrograph with a magnification of 100 diameters.

On a strict Sippy ulcer regime, with the administration of alkalies, the patient became symptom-free within a few days, and from then on had no subjective symptoms. He never complained of nausea, and there was no vomiting at any time, which was difficult to explain in view of subsequent findings. However, the red blood count and the hemoglobin continued to fall, reaching their lowest level at 2,730,000 red blood cells, with a hemoglobin of 49 per cent. A total of six blood transfusions was given, but the red blood count on 13 occasions during the preoperative period never became elevated above 4,300,000 cells per cubic millimeter.

The first gastrointestinal roentgen-ray study was made on September 1, 1936, and revealed an inability to fill out the duodenal cap. Fluoroscopically there was a constant deformity and irregularity of the cap on the films, but no typical ulcer niche was demonstrated. It was significant to note that there was an absence of any six

hour retention of barium in the stomach. A double-contrast barium enema study was negative.

In view of this apparently confirmatory roentgen-ray finding, treatment for a bleeding duodenal ulcer was continued. The stools, however, remained strongly positive for occult blood, and the secondary anemia persisted.

The *second* roentgen-ray study, on September 14, 1936, showed some improvement in the appearance of the duodenal cap, and there was still an absence of gastric retention at the end of six hours. No filling defect in the small intestinal tract was demonstrated beyond the duodenal cap.

At this point further medical treatment was deemed inadvisable, so, following a surgical consultation, laparotomy was performed by Dr. William Bates on September

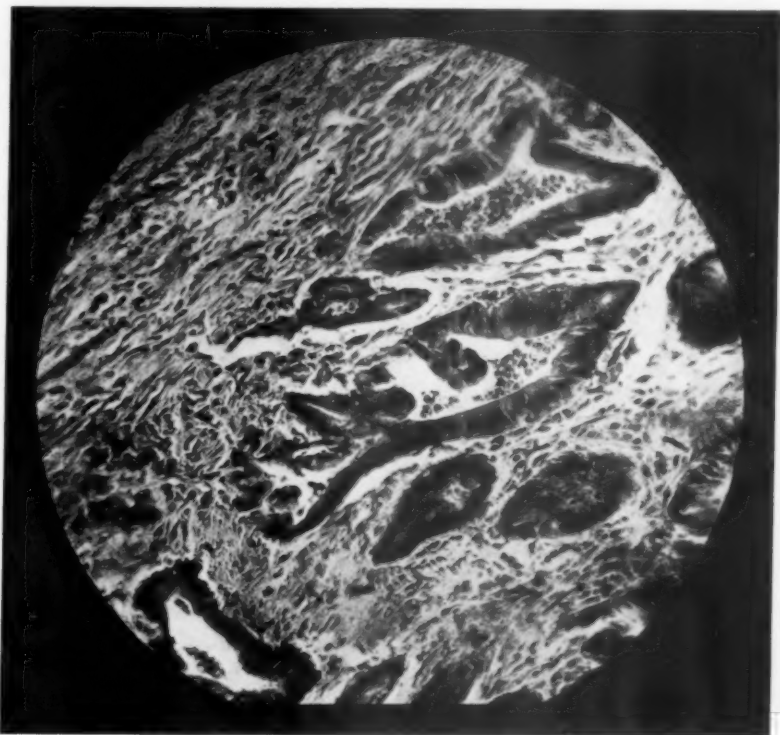


FIG. 3. Section of the tumor mass, reduced from a photomicrograph with a magnification of 450 diameters.

18, 1936. A constricting *annular carcinoma of the jejunum* was found 20 centimeters distal to the ligament of Treitz (figure 1), the lumen through the lesion measuring 1 centimeter in diameter. Many of the regional mesenteric lymph nodes were found to be enlarged, and there was one small nodule on the under-surface of the liver. The stomach and duodenum were normal, there being no evidence whatever of ulcer. The operation consisted of a resection of 11 centimeters of the jejunum with an end-to-end anastomosis. Several of the attached enlarged mesenteric lymph nodes were removed for biopsy.

The pathological report was as follows: Specimen consists of a section of the jejunum 11 centimeters in length with the attached mesentery and lymph nodes. In the middle portion of the section is a completely encircling growth which is 3 centi-

meters in width, obstructing the lumen so that it was only 1 centimeter in diameter through the lesion. The surface of the same has smooth and roughened areas. The cut surface has a pale pink color and is homogenous. In the attached mesentery there are several small, firm lymph nodes. *Microscopic:* Sections through the intestinal wall and mass show normal mucosa ending abruptly at the mass which is composed almost entirely of large and small irregular shaped glandular structures supported by a small amount of fibrous tissue (figure 2). The lining epithelium is tall columnar but the cells vary in size and the nuclei have lost their polarity (figure 3). The nuclei vary in size, shape and density of staining. No mitoses seen. The supporting stroma is infiltrated by eosinophiles. The glands do not invade the muscularis. The lymph nodes do not show any evidence of metastasis. *Diagnosis:* Primary adenocarcinoma of jejunum.

The patient made a very successful postoperative recovery, and was discharged from the hospital October 7, 1936, three weeks following operation. Since then improvement has been steady, he has been symptom-free, is gaining weight, and has returned to work. Deep roentgen-ray therapy has been given regularly since. A gastrointestinal roentgen-ray study, on December 10, 1936, showed a normal passage of barium through the jejunum. He was last seen on April 27, 1937; at that time he had gained 11 pounds since the operation, was symptom-free and having normal bowel movements with the use of mineral oil. Examination of the abdomen revealed no tenderness, no palpable induration and the liver was not palpable. Systolic blood pressure was 130 mm. of mercury and diastolic 80 mm. Hemoglobin was 84 per cent and red blood cells 4,600,000. Stool specimens were negative for occult blood.

Note: Since this case report was submitted, the patient has been seen on several occasions, the last examination having been made on June 13, 1938. At that time he showed a further increase in weight, was entirely symptom-free, and bowel function was normal. The blood count was also normal. Abdominal examination again revealed no palpable enlargement of the liver, and no intra-abdominal mass.

SUMMARY

1. Primary carcinoma of the jejunum is of interest because of its extreme rarity of occurrence.
2. The lesion is usually of the annular, constricting, adenomatous type.
3. The average duration of symptoms is about one to one and one-half years.
4. The earliest symptoms are systemic in character, namely, weakness, weight loss and fatigability, accounted for by the constant blood loss with a resulting secondary anemia.
5. The persistent presence of occult blood in the stools, otherwise unaccounted for, should lead to the suspicion of possible malignancy of the small bowel.
6. The more advanced symptoms and signs are in relationship to the degree of intestinal obstruction.
7. The vomiting of large amounts of grayish green fluid containing bile and food particles is suggestive of obstruction near the ligament of Treitz.
8. An abdominal mass is usually not palpable until after metastasis occurs.
9. Metastasis occurs late and distant metastases are relatively uncommon.
10. Radical resection with an end-to-end or side-to-side anastomosis is the surgical procedure of choice.
11. The prognosis is poor. The hope for improved prognosis lies in the earlier establishment of the diagnosis, by means of improved technic in the roentgen-ray study of the small intestinal tract.
12. A typical case diagnosed at operation is reported.

REFERENCES

1. CARTER, R. F.: Carcinoma of the jejunum, report of three cases, *Ann. Surg.*, 1935, cii, 1019-1028.
2. NETTROUR, W. S.: Carcinoma of the jejunum, report of a case, *Proc. Staff Meet. Mayo Clin.*, 1936, xi, 356-360.
3. RANKIN, F. W., and MAYO, C., 2ND: Carcinoma of the small bowel, *Surg., Gynec. and Obst.*, 1930, I, 939-947.
4. JOHNSON, R.: Carcinoma of the jejunum and ileum, *British Jr. Surg.*, 1922, ix, 422.
5. RAIFORD, T. S.: Tumors of small intestine, *Arch. Surg.*, 1932, xxv, 122.
6. NEWTON, F. C., and BUCKLEY, R. C.: Primary adenocarcinoma of the jejunum, report of two cases, *New Eng. Jr. Med.*, 1930, ccii, 255-261.
7. CAVE, H. W.: Carcinoma of the jejunum, report of three cases, *Ann. Surg.*, 1935, cii, 1097-1101.
8. CLARK, E. D.: Carcinoma of the small intestine, *Surg., Gynec. and Obst.*, 1926, xliii, 757-763.
9. HELLSTRÖM, JOHN: Primary cancer of the jejunum and ileum, *Acta. Chir. Scandinav.*, 1927, lxii, 465.

EDITORIAL

STATE PSYCHOPATHIC HOSPITALS

THE general medical profession has a definite interest in the construction by the State of new types of hospital facilities. Since there is an active movement on foot towards the construction of psychopathic hospitals in a number of states not yet possessing such units, a discussion of some of the problems involved may be of value.

A psychopathic hospital, as distinguished from a state or private hospital for the care of mental patients, or an insane asylum in the older terminology, may be defined as an institution to which patients presenting symptoms of mental disease are admitted for intensive diagnostic study or for a brief period of treatment, but not for permanent institutional care. Such institutions are also considered to have both research and educational functions.

The first question that arises in connection with the establishment of a State Psychopathic Hospital is whether this unit should serve as a receiving hospital for the other State Mental Hospitals. It is a disputed point. It is obvious that each new admission to any mental institution should be thoroughly surveyed both physically and mentally, to determine as accurately as possible the pathogenesis of the mental symptoms present and to furnish a basis for a program of therapy. It is also conceded that the organization and equipment of a psychopathic hospital are ideally fitted for this task. There are, however, definite disadvantages to be considered. In the first place the number of admissions to the State Mental Hospitals in the average state is very large. To pass all of these through the psychopathic hospital and still maintain a high standard of work in this institution would require a very large psychopathic hospital—which in view of the high maintenance cost of such institutions is not feasible in most states. Furthermore, by this plan the large mental hospitals of the state would receive all their patients with a sheaf of reports from the Psychopathic Hospital; if they repeated the work done they would be unnecessarily duplicating expensive procedures and if they did not they would be limiting themselves, to a considerable degree, to the task of custodial care. It is certainly vital that the work of physicians in the large mental hospital include experience in the diagnostic survey of new patients. Moreover, from the point of view of the State Psychopathic Hospital there would be a serious disadvantage in handling all the new cases of the state for inevitably the pressure of admissions would enforce a rapid turnover which in turn would tend towards routine types of study, towards decrease in the length of the period of observation, and towards insufficient time for careful investigation of new diagnostic and therapeutic procedures. Finally the admission of all new cases to the State Psychopathic Hospital would entail moving many

of these cases very considerable distances from the far corners of the state only to have to return many of them for definitive treatment to the State Mental Hospital nearest to their homes.

An admissions policy for the State Psychopathic Hospital which seems to combine service to the community, to the other State Mental Hospitals, and to its own educational and research functions may be somewhat arbitrarily outlined under the following heads:

(1) The State Psychopathic Hospital should admit, as far as its capacity permits, all such unusually puzzling or complicated cases as are referred to it, because of its special diagnostic facilities and its consultant connections, from the admitting offices of State Mental Hospitals.

(2) The State Psychopathic Hospital should admit directly cases from its own Out-Patient Department or referred to it by outside physicians for voluntary commitment if such cases are thought to require hospitalization.

(3) Acute temporary mental conditions (deliria, etc.) arising in patients on medical and surgical wards of general hospitals may necessitate the removal of such cases for the sake of the other patients. In such instances the Psychopathic Hospital, if within reasonable distance, will offer a better combination of medical and psychiatric care than is usually available in a State Mental Hospital. It should be its policy to admit such emergency cases.

(4) Patients whose own attitude, or that of their family, renders commitment to a State Mental Hospital difficult, may be cared for in the State Psychopathic Hospital under some modified form of voluntary commitment. Similarly many cases of psychoneurosis that do not need commitment may with profit to themselves be studied and treated in a Psychopathic Hospital.

(5) Cases of mental disease applying for State care which fall into those groups which are being actively investigated in the State Psychopathic Hospital should be referred to this hospital for admission.

There is very little question but what a Psychopathic Hospital should, if possible, be constructed in close physical connection with a large general hospital. The laboratory, roentgenologic, operating room and other facilities of the latter may thus cover the needs of the psychiatric unit. Moreover, the various specialties of medicine each with its diagnostic and therapeutic armamentarium will be represented in the general hospital and this material together with the specialist personnel will add greatly to the possibilities of a high standard of medical care for the patients of the Psychopathic Hospital.

If there is a state-supported or state-owned medical school in the state then certainly it should be as the psychiatric unit of the general hospital of the state medical school that the State Psychopathic Hospital should function. The tremendous advantage is thus gained of utilizing this institution to educate the future physicians of the state in the principles of preventive and curative psychiatry. The integration of the psychiatric unit with the other

clinical departments of the hospital—the close relationship between the psychiatric out-patient clinic and the other out-patient clinics—the utilization of psychiatric consultants on the medical and surgical wards, and of medical and surgical or specialist consultants on the psychiatric wards—all these tend towards a more rational conception on the part of students and staff of the general hospital of the powers and the limitations of modern psychiatric methods—and towards closer reasoning and better acquaintance with disease among the psychiatrists.

The educative functions of the Psychopathic Hospital are of course not confined to the students and staff of its affiliated general hospital. The time is certainly coming when hospital and out-patient experience with mental patients, especially in the earlier stages of their illness, will be a requisite for satisfactory training for internal medicine. Such graduate students of medicine will fill many of the interns positions in the psychopathic hospitals. The junior nurses also will come from the Training Schools which require psychiatric nursing experience. The psychiatric staff of such a state institution will naturally also take part in any campaign of lay instruction in mental hygiene.

In relation to research also there is an obvious advantage in close affiliation between the State Psychopathic Hospital and the State Medical School. The laboratories of the school, with their specialized personnel and equipment, would greatly influence and sustain the research endeavors of the psychiatrists. It should be the function of such a psychopathic hospital not only to do what it can to add to psychiatric knowledge, but especially to be the proving ground for the other State Mental Hospitals for new diagnostic technics and for new and promising methods of treatment.

When no medical school is available the State Psychopathic Hospital will possess somewhat less educational value and fewer research resources. It will strengthen itself by an alliance with any large public or voluntary general hospital, but should no doubt retain its autonomy as a part of the State Mental Hospital system. However, when it is closely integrated with the state medical school hospital it is probably best that it be considered an integral part of that hospital, administered by the director of that hospital, staffed by the Department of Psychiatry of that school, but working by definite agreements in full coöperation with the State Mental Hospital system.

REVIEWS

Tuberculosis of the Lymphatic System. By RICHARD H. MILLER, M.D., F.A.C.S., Assistant Professor of Surgery, Harvard Medical School; Associate Surgeon, Massachusetts General Hospital. 248 pages; 22 × 15 cm. The Macmillan Co., New York. 1934. Price, \$4.00.

In spite of the fact that tuberculosis of the lymph glands is growing steadily less common in this country, it still frequently presents a clinical problem to the practitioner. The author has worked for years in the Non-Pulmonary Tuberculosis Clinic of the Massachusetts General Hospital and the clinical aspects of the book are based upon this experience. There is an interesting historical account of scrofula and of the present incidence of glandular tuberculosis in different parts of the world. The author feels that the eradication of tuberculous cattle, the pasteurization of milk, the early extirpation of tonsils and adenoids and the more effective segregation of active human cases of tuberculosis have been the chief factors responsible for the decrease of glandular tuberculosis. He discusses the clinical features presented by tuberculosis in the different glandular groups in the body and their complications. The results with various modes of therapy, surgery, tuberculin heliotherapy, irradiation, etc., are analyzed and figures presented. Radical excision where feasible is favored. Of particular interest is the description of the routine employed in the investigation of the patient's family, home and occupation and the regulations advised in relation to contagiousness.

It is a valuable small monograph for all internists.

M. C. P.

The Lung. By WILLIAM SNOW MILLER, M.D., Sc.D. 209 pages; 10 × 16½ cm. Charles C. Thomas, Springfield, Ill. 1937. Price, \$7.50.

The medical profession owes to a group of Dr. Miller's friends the opportunity of possessing in a single volume the gist of his many years of anatomical research on the structure of the lung. To internists who are interested in the rapidly advancing field of the mechanics of respiratory disease the basic facts concerning the construction of the bronchial tree and the alveoli, their blood and lymph supply, and their pleural covering will be of keen interest. As a reference book it will meet a wide demand. The illustrations in color of reconstructions of anatomical detail are very helpful; and the numerous other illustrations greatly increase the value of the book. The historical note on the work of those investigators who contributed most to our knowledge of lung structure is very illuminating. The volume should be in the library of all students of pulmonary disease.

M. C. P.

Heart Disease in General Practice. By PAUL D. WHITE, A.B., M.D., Assistant Professor of Medicine, Harvard University Medical School; Edited by MORRIS FISHBEIN, M.D. 338 pages; 19.5 × 13 cm. National Medical Book Co., Inc., New York. 1937. Price, \$3.00.

Dr. White has written this small manual in the form of questions and answers. He has grouped these under the following main headings: Historical Introduction; Diagnosis; Prognosis; Treatment. There are numerous subdivisions under each heading. For instance under diagnosis there are sections on symptoms, signs, blood pressure, electrocardiography, etc. The questions are highly practical. Is there such a condition as acute dilatation of the heart? Is syncope due to heart disease

or heart weakness? What disorders of cardiac function are important and what unimportant?

Not every good teacher can employ the Socratic method to advantage. Dr. White can. The book is worth reading and rereading. It is small, light and inexpensive, moreover, and these qualities should extend its circulation.

M. C. P.

Why We Do It. By EDWARD C. MASON, M.D. 177 pages; 20 × 13.5 cm. C. V. Mosby Co., St. Louis. 1937. Price, \$1.50.

The author has written a small book for the laity in which he discusses in a simple way some of the fundamental psychiatric conceptions as to the interests which affect human conduct, the development of personality, the sexual factor, social development, and the neuroses and psychoses. The lay reader will find it not only interesting, but wholly intelligible and in many instances helpful. It will be read with profit by medical students in their first year, and by older students of medicine who graduated without grace of psychiatric instruction.

M. C. P.

Step by Step in Sex Education. By EDITH HALE SWIFT, M.D. 207 pages. The Macmillan Co., New York. 1938. Price, \$2.00.

This book should be very welcome to those of us who are called upon to advise parents as to how they should discuss sex with their children. The author is a Visiting Lecturer at Wayne University and Director of the Family Consultation Service, Detroit. It is obvious from the book that she has had considerable experience in advising about sex education.

The unique feature about the book is that all the material is presented as imaginary dialogues or discussions. The four characters used are a mother, father, son and daughter. The parents started teaching the children from the age of two years and carry them up to twenty years. No parent is expected to follow any part in detail, but parents who read the book through will learn principles which can guide their answers to their children's questions. The most important topics are adequately covered. The basic principle on which the book is written is one of frank, unembarrassed handling of any topic, with a minimum of moralizing. In this respect the book measures up to the best standards of progressive education and mental hygiene.

H. W. N.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library are gratefully acknowledged:

- Dr. Louis Faugeres Bishop, Jr., F.A.C.P., New York, N. Y.—2 reprints;
Dr. Perk Lee Davis (Associate), Philadelphia, Pa.—3 reprints;
Dr. Leon S. Gordon (Associate), Washington, D. C.—1 reprint;
Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Lemuel C. McGee, F.A.C.P., Elkins, W. Va.—11 reprints;
Dr. Gordon B. Wilder (Associate), Anderson, Ind.—1 reprint.

Mrs. Cary T. Grayson, Washington, D. C.—Publication, "In Memoriam," containing reprints of articles appearing in the "Red Cross Courier" for March, April and May, 1938, on the life and works of the late Admiral Cary T. Grayson (Associate).

United Hospital Fund, New York, N. Y.—1 book, "Report of the Hospital Survey for New York," Volume III, 1938.

DR. MOHLER APPOINTED DEAN OF JEFFERSON MEDICAL COLLEGE

Dr. Henry K. Mohler, F.A.C.P., Medical Director of the Jefferson Medical College Hospital of Philadelphia for the last twenty-four years, assumed new duties as Dean of the College on August 1, having been elected to this post by the board of trustees of the College on June 13.

Dr. Mohler was graduated from Jefferson Medical College in 1912 and the same year received his appointment to the resident staff of Jefferson Hospital. He became Medical Director of the Hospital in 1914, and was also named assistant physician to the Hospital.

During 1913-14, he was in charge of the laboratory of clinical medicine in Jefferson Medical College and was elected instructor in medicine from 1913 to 1922. From 1922 to 1925 he was demonstrator in medicine, and in September, 1925, was elected associate in medicine, a post he held until 1929. He was elected assistant professor of medicine, November, 1929; associate professor of medicine in March, 1932; and clinical professor of therapeutics, June 30, 1936.

Dr. Mohler is also a graduate of the Philadelphia College of Pharmacy, and held the highest general average in his senior year and was awarded five prizes. When graduated from Jefferson Medical College, he held the highest general average in his senior year, was president of his senior class and was awarded five prizes.

Dr. Mohler is a member of many scientific medical societies, a past president of the Philadelphia Heart Association, a past president of the Pennsylvania Hospital Association, and has been a Fellow of the American College of Physicians since 1923.

Dr. E. J. G. Beardsley, F.A.C.P., Philadelphia, was the guest of the Northumberland County Medical Society June 9, 1938, and conducted a clinic at the Packer Hospital at Sunbury, Pa., and subsequently a round table discussion concerning the clinical material presented.

Mercy Hospital, Chicago, has recently become University Hospital of Loyola University School of Medicine. It will be known henceforth as Mercy Hospital, Loyola University Clinics. Dr. Robert S. Berghoff, F.A.C.P., Chicago, has been appointed Medical Director of the institution.

Dr. Louis F. Bishop, Jr., F.A.C.P., New York, N. Y., addressed the Association for the Advancement of Industrial Medicine at New York City, May 18, 1938, on "Cardiovascular Syphilis."

Dr. Bishop spoke on "Historical Landmarks of Cardiology" on May 2, 1938, before the Pre-Medical Society, the College of the City of New York.

Dr. Warren Coleman, F.A.C.P., New York City, will retire from the practice of medicine in New York City and remove to Augusta, Ga., on October 1. It is probable that he will continue in consultation work and teaching at the University of Georgia School of Medicine.

The Eleventh Annual Graduate Fortnight of the New York Academy of Medicine will be held October 24 to November 4, 1938, on "Diseases of Blood and Blood-Forming Organs." The program comprises afternoon clinics, evening meetings and scientific exhibits. Among those scheduled to present papers at the evening sessions are:

Dr. George R. Minot, F.A.C.P., Boston: "Etiology, Diagnosis and Treatment of Macrocytic Anemia" and "Other Forms of Hypochromic Anemia";

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor: "Liver Therapy in Macrocytic Anemia";

Dr. Russell L. Haden, F.A.C.P., Cleveland: "Diagnostic Significance of Changes in Erythrocytes";

Dr. Claude E. Forkner, F.A.C.P., New York: "Common and Unusual Types of Leukemia."

Dr. George M. Decherd, Jr., F.A.C.P., has terminated his appointment as Assistant Professor of Medicine at Louisiana State University Medical Center, New Orleans, to accept the appointment as Associate Professor of Medicine at the University of Texas School of Medicine at Galveston.

At a meeting of the Brooklyn Society of Internal Medicine May 27, 1938, Dr. Henry Monroe Moses, F.A.C.P., was elected President and Dr. Henry Dana Fearon, F.A.C.P., was reelected Treasurer for 1938-39. Dr. Moses succeeds Dr. Frank Bethel Cross, F.A.C.P.

Dr. Anthony Bassler, F.A.C.P., New York City, was awarded the honorary degree of Doctor of Laws by Hahnemann Medical College of Philadelphia at its annual convocation in June. Dr. Carl C. Fischer, F.A.C.P., Philadelphia, was awarded the honorary degree of Master of Arts.

The Fourth Annual Symposium was presented by the Golden Clinic of the Davis Memorial Hospital, Elkins, W. Va., June 25, 1938, with Dr. R. J. Condry, F.A.C.P., acting as chairman of arrangements. Dr. Oscar B. Biern, F.A.C.P., Huntington, W. Va., acted as a leader of a round table discussion at the West Virginia Heart Association Luncheon and Dr. Lester Hollander, F.A.C.P., Pittsburgh, gave a paper on "Dermatological Problems of the General Practitioner." Dr. Lemuel C. McGee, F.A.C.P., is the internist to the Golden Clinic.

Dr. J. Walter Torbett, Jr. (Associate), formerly of Marlin, Texas, has accepted an appointment in the Department of Medicine at Louisiana State University Medical Center, New Orleans, as of July 1.

Dr. William G. Herrman, F.A.C.P., President of the Medical Society of the State of New Jersey, delivered one of the principal addresses in connection with the dedication of the new administration building and central unit of Bergen Pines, Bergen County Hospital, at Ridgewood, N. J., on May 8.

At the first annual meeting of the Iowa Pediatric Club, held in Des Moines, April 8, the guest speaker was Dr. Julius H. Hess, F.A.C.P., Chicago, on "Chicago's Program for the Care of Premature Babies." Other speakers included Dr. Walter L. Bierring, F.A.C.P., Des Moines, on "The National Program on Maternal and Child Health" and Dr. Fred Sternagel (Associate), West Des Moines, who conducted a symposium on epidemic sore throat and scarlet fever.

Dr. Harold W. Gregg, F.A.C.P., Butte, Mont., was elected president-elect of the Medical Association of Montana at its last annual session during April.

Dr. Rufus Cole, F.A.C.P., Director of the Hospital of the Rockefeller Institute, New York City, since 1909, was awarded the George M. Kober Medal for distinguished service to medicine by the Association of American Physicians at its last annual meeting during May.

Dr. James Buren Sidbury, F.A.C.P., Wilmington, N. C., was installed as President of the Medical Society of the State of North Carolina at its annual meeting during May.

Among those who presented papers on the program of the twenty-second annual scientific session of the Association for the Study of Internal Secretions at San Francisco, June 13-14, were Dr. Daniel V. Conwell, F.A.C.P., and Dr. Clarence J. Kurth, Halstead, Kan., "Insulin Therapy in Mental Diseases"; Dr. Henry H. Turner, F.A.C.P., Oklahoma City, "Infantilism with Congenital Webbed Neck and Cubitus Valgus"; Dr. Willard O. Thompson, F.A.C.P., Dr. Phebe K. Thompson, Dr. Samuel G. Taylor, III (Associate) and Dr. William S. Hoffman (Associate), Chicago, "The Treatment of Addison's Disease with Adrenal Cortex Extract."

Dr. William J. Kerr, F.A.C.P., San Francisco, delivered the presidential address on "Radiculitis Associated with Spinal Arthritis" before the annual meeting of the American Rheumatism Association at San Francisco, June 13. Other speakers included Dr. Mark P. Schultz, F.A.C.P., Washington, D. C., "Metabolic Factors in the Induction of Nonpurulent Carditis"; and Dr. Walter Bauer, F.A.C.P., Boston, "Treatment of Gonorrheal and Rheumatoid Arthritis with Sulfanilamide."

Dr. Jay A. Myers, F.A.C.P., Minneapolis, delivered the presidential address before the meeting of the American Academy of Tuberculosis Physicians at San Francisco, June 17-18. Other speakers on the program included Dr. Charles W. Mills, F.A.C.P., Tucson, Ariz., "A Case of Fungus Coccidioides Infection Primarily in the Lung with Cavity Formation and Healing"; Dr. John M. Nicklas (Associate), Valhalla, N. Y., "The Tuberculous Child"; and Dr. Maxim Pollak, F.A.C.P., Peoria, Ill., "Results of Effective Tuberculosis Control."

Dr. James S. McLester, F.A.C.P., participated in a symposium on oxygen therapy before the Jefferson County (Ala.) Medical Society, May 16, his subject being, "Clinical Response to Oxygen Therapy."

Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, was awarded the Mendel Medal for 1938 by Villanova (Pa.) College recently in recognition of his scientific approach to the problems of public health.

Dr. William J. Mallory, F.A.C.P., Washington, D. C., was inducted May 11 as President of the Medical Society of the District of Columbia. Dr. Coursen B. Conklin, F.A.C.P., was reelected secretary.

Dr. M. C. Pincoffs, F.A.C.P., Professor of Medicine, University of Maryland School of Medicine, Baltimore, and Dr. Beverley R. Tucker, F.A.C.P., Professor of Neuropsychiatry, Medical College of Virginia, Richmond, were among the instructors participating in the sixth annual graduate short course for physicians held at Daytona Beach, Fla., June 27 to July 2, under the auspices of the Florida Medical Association and the Florida State Board of Health.

Dr. Victor F. Cullen, F.A.C.P., State Sanatorium, Md., has been made a vice president of the Medical and Chirurgical Faculty of Maryland.

Dr. Edward L. Turner, F.A.C.P., Nashville, Tenn., has been appointed President of Meharry Medical College, July 1, to succeed Dr. John J. Mullooney, who has retired.

Dr. Anita M. Mühl, F.A.C.P., San Diego, addressed the twenty-third annual convention of the American Medical Women's Association at San Francisco June 12-14, on "The Doctor's Mental Attitude."

Dr. Walter L. Treadway, F.A.C.P., Assistant Surgeon General of the U. S. Public Health Service, Washington, D. C., has been appointed medical officer in charge of the federal narcotic farm at Lexington, Ky.

Dr. Raymond J. Reitzel, F.A.C.P., and Dr. Stacy R. Mettier, F.A.C.P., have been promoted to Associate Clinical Professor of Medicine and Associate Professor of Medicine, respectively, in the University of California Medical School, San Francisco.

The Medical Association of Georgia has announced that the L. G. Hardman Loving Cup honor for the past year will go to Dr. Virgil P. W. Sydenstricker, F.A.C.P., Professor of Medicine, University of Georgia School of Medicine. This honor is awarded annually to the physician who is deemed to have rendered the most distinguished medical service during the previous year.

Dr. Reginald Fitz, F.A.C.P., Wade Professor of Medicine at Boston University School of Medicine, conducted a round table discussion and presented a paper on "The Case of the Forsaken Pamphlet" at the first anniversary celebration of the Gerrish Memorial Library, Lewiston, Maine, on May 26.

Dr. George C. Stucky, F.A.C.P., for many years Superintendent of the Ingham County Tuberculosis Sanatorium, Lansing, Mich., has resigned to work on a rural health project being conducted in seven counties of Michigan by the W. K. Kellogg Foundation.

On May 23 the Minnesota Public Health Association sponsored a testimonial dinner in honor of Dr. F. E. Harrington, F.A.C.P., Minneapolis, on the anniversary of the opening of the Lymanhurst Health Center, which he established seventeen years ago. Dr. Harrington was sent to Minneapolis in 1920 by the U. S. Public Health Service. He urged the early establishment of a school for tubercular children, and in 1921 Lymanhurst was built.

The Board of Regents of the University of Oklahoma recently announced the following appointments on the Faculty of Medicine:

- Dr. Hull Wesley Butler, F.A.C.P., Associate in Medicine and Associate in Histology;
 - Dr. Minard F. Jacobs (Associate), Instructor in Medicine;
 - Dr. Bert Fletcher Keltz, F.A.C.P., Associate in Medicine and Supervisor of Clinical Clerkships;
 - Dr. Elmer R. Musick (Associate), Associate in Medicine;
 - Dr. Frederick Redding Hood (Associate), Associate in Medicine;
 - Dr. William Ward Rucks, Jr. (Associate), Associate in Medicine;
 - Dr. Wilbur Floyd Keller (Associate), Associate in Medicine.
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Dr. Henry Kirvin Speed, F.A.C.P., is President (1938-39) of the Oklahoma State Medical Association.

Major General Charles R. Reynolds, F.A.C.P., Surgeon General of the U. S. Army, Washington, has been designated by President Roosevelt to act as president of the permanent committee of the International Congress on Military Medicine and Pharmacy, to be held in Washington during May, 1939.

Dr. F. M. Acree, F.A.C.P., Greenville, Miss., is the Secretary-Treasurer of the Delta Medical Society.

Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., has been elected President of the State and Provisional Health Authorities of North America.

Dr. Henry A. Christian, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, was the chief speaker on the centennial program of the Medical College of Virginia at Richmond on June 7.

Dr. Robert S. Palmer, F.A.C.P., Boston, addressed the University of Virginia Medical Society recently on "Rationale and Results of the Surgical Treatment of Essential Hypertension."

Dr. Walter B. Martin, F.A.C.P., Norfolk, is the chairman of the medical section of the Virginia Academy of Science.

Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., was made President-Elect of the American Medical Association at its San Francisco meeting in June. Dr. Sleyster had previously served as Secretary, President and Treasurer of the Wisconsin State Medical Society, as Editor of the Wisconsin Medical Journal, as delegate to the House of Delegates of the American Medical Association for the Wisconsin State Medical Society and as a member (for two years chairman) of the Board of Trustees of the American Medical Association.

Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., was reelected to the Council on Scientific Assembly until 1943.

Dr. Nathan B. Van Etten, F.A.C.P., New York, N. Y., was succeeded as the speaker of the House of Delegates by Dr. Harrison H. Shoulders of Nashville, Tenn.

Dr. Edward Weiss (Fellow) was a member of the group representing the Temple University Medical School which was awarded the Gold Medal for the exhibit on Cardiovascular-Renal Diseases at the recent meeting of the American Medical Association.

Dr. M. Hill Metz (Associate) presented a paper, "Peptic Ulcer Treated by Posterior Pituitary Extract—Two Years Experience," at the annual session of the Texas State Medical Association, Galveston, on May 10, 1938.

OBITUARY

DR. GEORGE CAPLICE MILLER

Dr. George Caplice Miller, of Seattle, died April 2, 1938, of acute leukemia, following an illness of less than one month.

Dr. Miller, the son of a physician, was born in St. Marys, Kansas, December 17, 1886. He was graduated from St. Louis University Medical School in 1909 and after his internship he was associated in practice with Dr. William Engelbach for some time. In 1917, he entered the army and served for the duration of the war.

In 1919 he located in Seattle and for a few years was associated with a clinic, after which he practiced independently until his death.

Dr. Miller had an unusually busy practice but he found time for a great deal of charity work, particularly in connection with Catholic organizations and with the Providence Hospital. He had been chief of staff of the Providence Hospital and his counsel was an important factor in the improvement of standards in that institution.

Ever since the opening of the new King County Hospital in 1931, he had been chief of the medical division, a task to which he gave much time and thought.

He is survived by his widow Mrs. Helen Miller, two daughters and two sons.

An unusually capable physician, a fine gentleman, he was widely known and he will long be remembered by the profession and the laity. His death was the occasion of an editorial in a local paper, an indication of the important place he held in this community.

C. E. WATTS, M.D.,
Governor for Washington